National Institute for Health and Care Excellence

Draft for consultation

Cerebral palsy in adults

[A3] Management of abnormal muscle tone: treatments to reduce dystonia

NICE guideline <TBC>

Evidence reviews

July 2018

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Management of abnormal muscle tone in adults aged 19 and over with cerebral palsy

Review question

A3 Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB)) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?

Introduction

Dystonia is a pattern of sustained disturbed muscle contraction causing abnormal posture and frequent involuntary movements in some adults with cerebral palsy. There can be environmental, physical or psychological factors that aggravate dystonia and once they have been removed there are enteral and intramuscular pharmacological agents that can be used to manage dystonia. Neurosurgical procedures, such as intrathecal baclofen therapy, and in severe intractable cases Deep Brain Stimulation (DBS) are currently available options. Both procedures require anaesthetic, and have surgical, recovery and long-term risks. This review question examines the effectiveness of these interventions, including patient experience and quality of life and in the case of DBS the potential complications of brain surgery as well as on-going maintenance costs.

PICO table

Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults aged 19 and over with predominantly dystonic cerebral palsy
Intervention	Pharmacological: • Levodopa • Anticholinergic drugs (trihexyphenidyl) • Botulinum toxin injections with adjunct treatments such as lycra and splint casting • Botulinum toxin injections without adjunct treatments • Gabapentin/ pregabalin • Tetrabenazine Non-pharmacological: • Deep brain stimulation • Intrathecal baclofen • Orthotics for physical function (dynamic orthotics [lycra])
Comparison	• Each other • Placebo • Usual care
Outcome	**Critical** • Health related quality of life

	• Dystonia • Patient or carer reported satisfaction **Important** • Motor function using functional measures • Goal attainment scores • Adverse events • Pain

For full details see the review protocol in appendix A

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines 2014: the manual. Methods specific to this review question are described in the review protocol in appendix A and for a full description of the methods see supplementary document C.

Declaration of interests were recorded according to NICE's 2014 conflicts of interest policy from May 2016 until April 2018. From April 2018 onwards they were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Interests Register).

Clinical evidence

Included studies

Five studies (number of participants, N=51) were included in the review: 1 randomised trial (Pozin 2014) and 4 before-and-after observational studies (Koy 2014, Marks 2011, Romito 2015, and Vidailhet 2009).

The clinical studies included in this evidence review are summarised in **Error! Reference source not found.** and evidence from these is summarised in the clinical evidence profiles (Table 3 and Table 4).

Pozin 2014 compared levodopa with placebo. The remaining studies (Koy 2014, Marks 2011, Romito 2015, and Vidailhet 2009) compared pre and post-operative outcomes in people receiving bilateral pallidal deep brain stimulation.

See also the literature search strategy in appendix B, study selection flow chart in appendix C, forest plots in appendix E and study evidence tables in appendix D.

Excluded studies

Studies excluded from this systematic review, with reasons for their exclusion, are provided in appendix K.

Summary of clinical studies included in the evidence reviewError! Reference source not found. provides a brief summary of the included studies.

Table 2: Summary of included studies

Study	Design	Participants	Comparison(s)	Outcomes
Koy 2014	Before-and-after study	N=8, age 16 to 33 years (mean 26 years), with dyskinetic CP. Germany	Bilateral pallidal deep brain stimulation: pre versus post-operative "on" or "off"	• Dystonia (follow up mean 3.7 years; range 9 months to 6.9 years)

Study	Design	Participants	Comparison(s)	Outcomes
Marks 2011	Before-and-after study	N=6, age 17 to 26 years (mean 21 years), with CP and dystonia unresponsive to pharmacological treatments. USA	Bilateral pallidal deep brain stimulation: pre versus post-operative	• Dystonia (follow up 6 months)
Pozin 2014	Randomised cross over trial	N=9, age 8 to 27 years (mean 17 years), with CP and bilateral dystonia disabling upper limb. Israel	Levodopa versus placebo	• Motor function using functional measures • Adverse events (follow-up 2 weeks)
Romito 2015	Before-and-after study	N=15, age 15 to 42 years (mean 30 years), with CP and persistent dystonia. Italy	Bilateral pallidal deep brain stimulation: pre versus post-operative	• Health related quality of life • Dystonia • Adverse events (mean follow up 4.4 years)
Vidailhet 2009	Before-and-after study	N=13, age 20 to 44 years (median 33 years), with CP dystonia unresponsive to pharmacological treatments. France	Bilateral pallidal deep brain stimulation: pre versus post-operative	• Health related quality of life • Dystonia • Adverse events • Pain (follow up 1 year)

CP: cerebral palsy; N: number of participants in study.

See appendix D for full evidence tables.

Quality assessment of clinical outcomes included in the evidence review

The clinical evidence profiles for this review question are presented in Table 3 and Table 4.

Table 3: Summary clinical evidence profile: Comparison 1: levodopa versus placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with Levodopa			
HRQoL - not reported	-	-	-	-	-
Dystonia - not reported	-	-	-	-	-
Satisfaction - not reported	-	-	-	-	-
Change in motor function from pre-treatment assessed with: QUEST score Scale from: 0 to 100 Follow-up: 2 weeks	The mean change in motor function from pre-treatment was -5.08 %	The mean change in motor function from pre-treatment in the intervention group was 5.92 % higher (1.72 lower to 13.56 higher)	-	9 (1 RCT)	Low [1,2]
Adverse events	No adverse events reported			9 (1 RCT)	Very low [1,3,4]
Goal attainment	-	-	-	-	-

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with Levodopa			
scores - not reported					
Pain - not reported	-	-	-	-	-

CI: confidence interval; HRQoL: health related quality of life; RCT: randomised controlled trial
1. Unclear randomisation method
2. Confidence interval for effect includes one default MID threshold
3. Adverse events were not systematically monitored.
4. No events reported

Table 4: Summary clinical evidence profile: Comparison 2: bilateral pallidal deep brain stimulation (DBS) – pre versus post-operative

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Risk - preoperative	Risk with Bilateral pallidal deep brain stimulation			
HRQoL assessed with: SF-36 General Health Scale from: 0 to 100 Follow-up: range 1 years to 4 years	The mean HRQoL was 67.31[1]	HRQoL after DBS ranged from 3.30 higher to 10.54 higher	-	28 (2 observational studies)	Very low[3]
HRQoL assessed with: SF-36 Physical Functioning Scale from: 0 to 100 Follow-up: range 1 years to 4 years	The mean HRQoL was 54.23[1]	HRQoL after DBS ranged from 3.46 higher to 30.00 higher	-	28 (2 observational studies)	Very low[3]
HRQoL assessed with: SF-36 Role (Physical) Scale from: 0 to 100 Follow-up: range 1 years to 4 years	The mean HRQoL was 56.92[1]	HRQoL after DBS ranged from 4.62 higher to 43.40 higher	-	28 (2 observational studies)	Very low[3]
HRQoL assessed with: SF-36 Role (Emotional) Scale from: 0 to 100 Follow-up: range 1 years to 4 years	The mean HRQoL was 35.89[1]	HRQoL after DBS ranged from 23.09 higher to 29.10 higher	-	28 (2 observational studies)	Very low[3]
HRQoL assessed with: SF-36 Social Functioning Scale from: 0 to 100 Follow-up: range 1 years to 4 years	The mean HRQoL was 64.42[1]	HRQoL after DBS ranged from 0.96 higher to 23.40 higher	-	28 (2 observational studies)	Very low [2,3]
HRQoL assessed with: SF-36 Body pain Scale from: 0 to 100 Follow-up: range 1 years to 4 years	The mean HRQoL was 61[1]	HRQoL after DBS ranged from 18.54 higher to 36.80 higher	-	28 (2 observational studies)	Very low[2]
HRQoL assessed with:	The mean HRQoL was	HRQoL after DBS ranged from 2.31 higher to 15.70 higher	-	28 (2 observational	Very low [3]

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Risk - preoperative	Risk with Bilateral pallidal deep brain stimulation			
SF-36 Vitality Scale from: 0 to 100 Follow-up: range 1 years to 4 years	51.15[1]			studies)	
HRQoL assessed with: SF-36 Mental health Scale from: 0 to 100 Follow-up: range 1 years to 4 years	The mean HRQoL was 56.62[1]	HRQoL after DBS ranged from 8.92 higher to 15.70 higher	-	28 (2 observational studies)	Very low[2]
Dystonia assessed with: Burke-Fahn-Marsden movement scale Scale from: 0 to 120 Follow-up: range 6 months to 4 years	The mean dystonia was 44.23[1]	Dystonia after DBS ranged from 7.60 lower to 35.40 lower	-	42 (4 observational studies)	Very low[2]
Dystonia assessed with: Burke-Fahn-Marsden disability scale Scale from: 0 to 30 Follow-up: range 6 months to 4 years	The mean dystonia was 12.58[1]	Dystonia after DBS ranged from 0.40 lower to 6.60 lower	-	42 (4 observational studies)	Very low[2]
Satisfaction - not reported	-	-	-	-	-
Motor function - not reported	-	-	-	-	-
Adverse events - Hypophonia Follow-up: 4 years	Rate was 2/15 (13%)		-	15 (1 observational study)	Very low[2,3]
Adverse events - Dysarthria Follow-up: 4 years	Rate was 4/15 (27%)		-	15 (1 observational study)	Very low[2,3]
Adverse events - Local pain Follow-up: range 1 years to 4 years	Rate ranged from 1/13 (8%) to 2/15 (13%)		-	28 (2 observational studies)	Very low[2,3]
Adverse events - Paraesthesia Follow-up: 4 years	Rate was 2/15 (13%)		-	15 (1 observational study)	Very low[2,3]
Adverse events - Anxiety Follow-up: 1 years	Rate was 5/13 (38%)		-	13 (1 observational study)	Very low[2,3]
Adverse events - Stimulation adjusted due to insufficient benefit Follow-up: 1 years	Rate was 4/13 (31%)		-	13 (1 observational study)	Very low[2,3]
Adverse events - Stimulator failure (exposure to magnetic field)	Rate was 1/13 (8%)		-	13 (1 observational study)	Very low[2,3]

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Risk - preoperative	Risk with Bilateral pallidal deep brain stimulation			
Follow-up: 1 years					
Goal attainment scores - not reported	-	-	-	-	-
Pain Follow-up: 1 years	The mean pain was 2.72	The mean pain in the intervention group was 0.93 lower (2.79 lower to 0.93 higher)	-	13 (1 observational study)	Very low[2]

CI: confidence interval; HRQoL: health related quality of life; SF-36: 36 items short from survey
1. Illustrative preoperative values taken from Vidailhet 2009
2. Downgraded for imprecision: number of participants < 400 or number of events < 300
3. No comparison group

See appendix F for the full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no studies were identified which were applicable to this review question.

Excluded studies

No studies were identified which were applicable to this review question.

Summary of studies included in the economic evidence review

No economic evaluations were included in this review.

Economic model

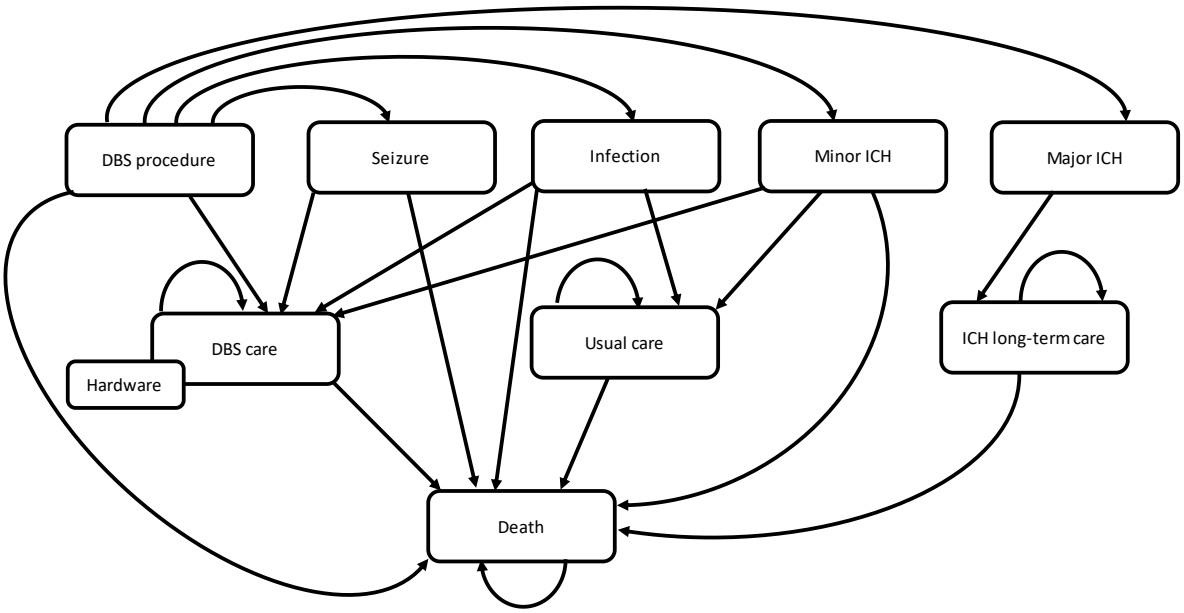
See appendix J for the full report of the economic model.

A decision analytical model in the form of a state transition model was developed to estimate the cost effectiveness of deep brain stimulation (DBS) compared to usual care of trihexyphenidyl 5mg daily in adults aged over 19 with cerebral palsy and dystonia. The main outcome of the economic model was incremental cost per QALY. Costing was undertaken using a NHS and Personal Social Services (PSS) perspective. The model had a lifetime time horizon. Costs and QALYs were discounted at 3.5% per annum.

During the procedure for DBS patients may experience a seizure, infection, intracranial haemorrhage (ICH), or die. Patients who experience an infection could either remain on DBS, or abandon DBS and receive “usual care”. Patients who experience a seizure or minor ICH remain on DBS treatment. Following a successful procedure for DBS, patients remain on DBS and receive a routine implanted pulse generator (IPG) replacement every 5 years. Each year patients on DBS are at risk of a hardware failure which will incur additional surgery to correct. Patients in usual care receive pharmacological treatment in the base case. It was assumed patients in usual care are not at risk of any adverse events.

The structure of the model is illustrated in Figure 1.

Figure 1: Model structure



Evidence identified during the accompanying clinical evidence review had small numbers and were not representative of adverse events seen in practice. Alternative papers that analysed DBS were sought to inform the probability of complications in the model. Two studies were identified Boviatsis 2010 and Voges 2006 reviewed the complications of DBS experienced by their departments; from 2003 to 2010 in 106 patients and from 1996 to 2003 in 262 patients, respectively. Both also compared their own results to others reported in the literature. The model assumed an annual probability of hardware failure of 4%. The probability of adverse events are listed in Table 5.

Table 5: Probability of perioperative DBS-related complications

Complication	Probability	Source and notes
Seizure	0.9%	Boviatsis 2010 stated that epileptic seizures can occur occasionally in patients undergoing DBS and reported a rate of 0.9% in their department. Voges also found a low risk in their review of the literature where 3 of the 7 studies reported cases of seizures (Beric 2001, 2.3%; Umemura 2003, 0.9%; Lyons 2004, 1.2%)
Infection first cycle	1.5%	Voges 2006 registered a total of 15 skin infections in 262 (5.7%) patients. The infection rate during the first observation period was 1.5% (4/262 patients) and the late infection rate after the initial surgery was 6.1% (11/180 patients). Voges 2006 concluded that their data are in line with infection rates given in the literature, ranging from 1.2% to 15.2%.
Infection second cycle	6.1%	
Remain on DBS following infection	20%	Three of those 15 patients in Voges 2006 were successfully treated with systemic antibiotics, but removal of the system was necessitated in the remaining 12.
Switch to usual care following infection	80%	
ICH minor	2.7%	Binder 2005: symptomatic with recovery (10/481) or asymptomatic (3/481)
ICH major	0.6%	Binder 2005: symptomatic with deficit (3/481)

Complication	Probability	Source and notes
Switch to usual care following minor ICH	23%	CT scanning instead of MRI was performed by Binder 2005 in 3 patients who had procedures aborted because of intraoperative neurological deficit (3/13)
Remain on DBS following Minor ICH	77%	It is not documented in Binder 2005 whether the other (10) intra-operative bleeds had their procedure aborted, or not. However, given that they could safely have a MRI, it is assumed DBS was completed (10/13).

CT: Computerised tomography; DBS: deep brain stimulation; ICH: intrathecal haemorrhage; MRI: Magnetic resonance imaging

Health related quality of life data was taken from 2 before and after type studies (Vidailhet 2009 and Romito 2015) that reported the results for each of the 8 domains of the SF-36, pre- and post- DBS treatment. Given heterogeneity in the results of the two studies they were used separately to inform the economic model. The SF-36 was mapped on to the EQ-5D, NICE's preferred measure of quality of life, for use in the economic model (discussed in detail in appendix J.) Given that no comparative data was identified, it was assumed the utility pre-DBS is equivalent to the utility associated with "usual care". It was also assumed that the utility post-DBS holds when patients remain on DBS care. A disutility was applied for patients undergoing surgery for DBS. A disutility was also applied for all adverse events in the model (Table 6). In the absence of evidence to the contrary overall survival was assumed identical between the two interventions considered.

Table 6: Disutility from DBS-related complications

Complication	Duration	Disutility (QALY loss)	Source
Procedure	2 weeks	-0.094 (-0.004)	Dolan 1997 (usual activities)
Hardware	1 week	-0.094 (-0.002)	Dolan 1997 (usual activities)
Infection	2 weeks	-0.123 (-0.005)	Dolan 1997 (pain/discomfort)
Seizure	1 day	(-0.001)	Lee 2013
ICH minor	2 weeks	-21.1%	Lip 2015
ICH major	6 weeks	-34.1%	Lip 2015
Long-term ICH care	Lifelong	-5.9%	Begum 2015

All DBS related resource use and unit costs were taken from Yianni 2005 and inflated to current costs. This was study of quality of life and costs in 26 patients with dystonia (not exclusively cerebral palsy) from 1 UK centre. The committee considered that costs reported in this paper maybe an underestimate of the true costs as they do not reflect the latest innovations in DBS. These costs were therefore explored extensively during sensitivity analysis.

Table 7: Cost of DBS reproduced from Yianni 2005

Cost component	Cost per patient, 2015/16
Preoperative assessment costs (consultation with a neurologist & 2-day inpatient stay with contact from a neuropsychologist)	£1,190
Surgery (staff costs, theatre time (3 hours), ward stay (10 days), MRI, CT, ECG, chest X ray)	£8,499
Stimulation equipment costs per surgical episode (Kinetra IPG, electrode lead, extension lead)	£15,432
Localisation equipment (planning station, stereotactic frame)	£2,214
Total cost of procedure	**£27,335**
Monitoring per year (1 neurosurgery outpatient visit, 3 specialist nurse visits, 3 neurology outpatient visits)	£863

DBS: deep brain stimulation; ICH: intrathecal haemorrhage.
1. HSHC inflations factor 1.3898 (2015/16 PPI 297/ 2002/03 PPI 213.7)

The annual costs of usual care were £77.82 and an annual follow up appointment in neurology at £161 taken from the NHS Electric Drug Tariff and NHS Reference Costs respectively.

A series of sensitivity analyses were undertaken in order to test how sensitive the results were to uncertainty in individual parameters. Probabilistic sensitivity analysis (PSA) was conducted in the model to take account of the simultaneous effect of uncertainty relating to model parameter values.

Results of the economic model

Base case results

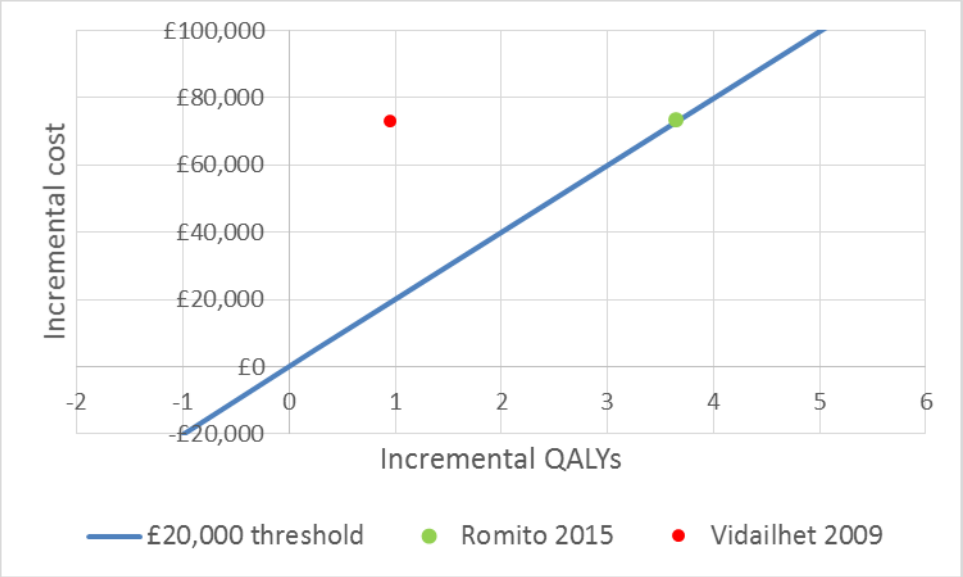
When Romito 2015 was used to inform the model, DBS was more costly and more effective than usual care, with an ICER of £20,169 per QALY (Table 8). DBS was also more costly than usual care when Vidailhet 2009 was used, but less effective than Romito 2015. As a result, the ICER was higher at £77,181 per QALY.

Table 8: Base case results (deterministic)

	Total costs	Total QALYs	ICER
Vidailhet 2009			
Usual care	£3,464	8.87	
DBS	£76,991	9.82	£77,181
Romito 2015			
Usual care	£3,464	5.01	
DBS	£76,991	8.66	£20,169

DBS: deep brain stimulation; ICER: Incremental cost effectiveness ratio; QALY: Quality-adjusted life year.

Figure 2: Cost-effectiveness plane (base case)



Sensitivity analysis results

The total QALYs increased for DBS when utility decrements were removed and when the risk of complications were removed. This reduced the ICER for Vidailhet 2009 and Romito 2015,

but the ICER for Vidailhet 2009 remained above NICE's upper threshold of £30,000 per QALY.

Reducing the time horizon reduced the number of QALYs that could be accrued and amplified the cost of the DBS procedure. This analysis increased the ICER above NICE's upper threshold in both studies.

When usual care consisted of botulinum toxin (a more costly treatment than trihexyphenidyl) the incremental cost reduced. This reduced the ICER for Vidailhet 2009 and Romito 2015, but the ICER for Vidailhet 2009 remained above NICE's upper threshold of £30,000 per QALY.

The results of each analysis are provided in Table 9 for Romito 2015 and Table 10 for Vidailhet 2009.

Table 9: Results of sensitivity analysis (Romito 2015)

	Total costs	Total QALYs	ICER
Disutility associated with DBS-related complications set to 0			
Usual care	£3,464	5.01	-
DBS	£76,991	8.66	£20,157
Probability of DBS-related complications set to 0			
Usual care	£3,464	5.01	-
DBS	£70,097	9.13	£16,163
Time horizon 4 years			
Usual care	£1,075	1.56	-
DBS	£40,995	2.80	£32,193
Treatment received in usual care			
Usual care	£17,572	5.01	-
DBS	£78,081[a]	8.66	£16,598

DBS: deep brain stimulation; ICER: Incremental cost effectiveness ratio;
QALY: Quality-adjusted life year.
2. Cost higher than the base case as some complications lead people to switch from DBS to usual care

Table 10: Results of sensitivity analysis (Vidailhet 2009)

	Total costs	Total QALYs	ICER
Disutility associated with DBS-related complications set to 0			
Usual care	£3,464	8.87	-
DBS	£76,991	9.83	£76,953
Probability of DBS-related complications set to 0			
Usual care	£3,464	8.87	-
DBS	£70,097	10.07	£55,610
Time horizon 4 years			
Usual care	£1,075	2.75	-
DBS	£44,956	3.07	£137,126
Treatment received in usual care			
Usual care	£17,572	8.87	-
DBS	£78,081[a]	9.82	£63,516

DBS: deep brain stimulation; ICER: Incremental cost effectiveness ratio;
QALY: Quality-adjusted life year.
(a) Cost higher than the base case as some complications lead people to switch from DBS to usual care

Using Romito 2015, the worst case scenario, raising the cost of the total procedure by 50%, increased the ICER to £23,918. In the best case scenario, lowering the total cost of the procedure by 50% reduced the ICER to £16,420. The most influential parameters were related to the replacement of the IPG. When the cost to replace the IPG was varied by 50% the ICER ranged from £16,342 to £23,750. When the frequency of replacements was changed from every 5 years to every 2 or 8 years, the ICER ranged from £16,761 to £33,351. (Figure 3, Figure 4) For Vidailhet 2009 all ICERs remained above a cost-effectiveness threshold of £30,000 per QALY when parameters were varied (Figure 5, Figure 6). Similarly to Romito 2015, the most influential parameters included the total cost of the procedure (namely stimulation equipment) and IPG replacements.

Figure 3: Tornado diagram of the costs associated with the procedure and monitoring (Romito 2015)

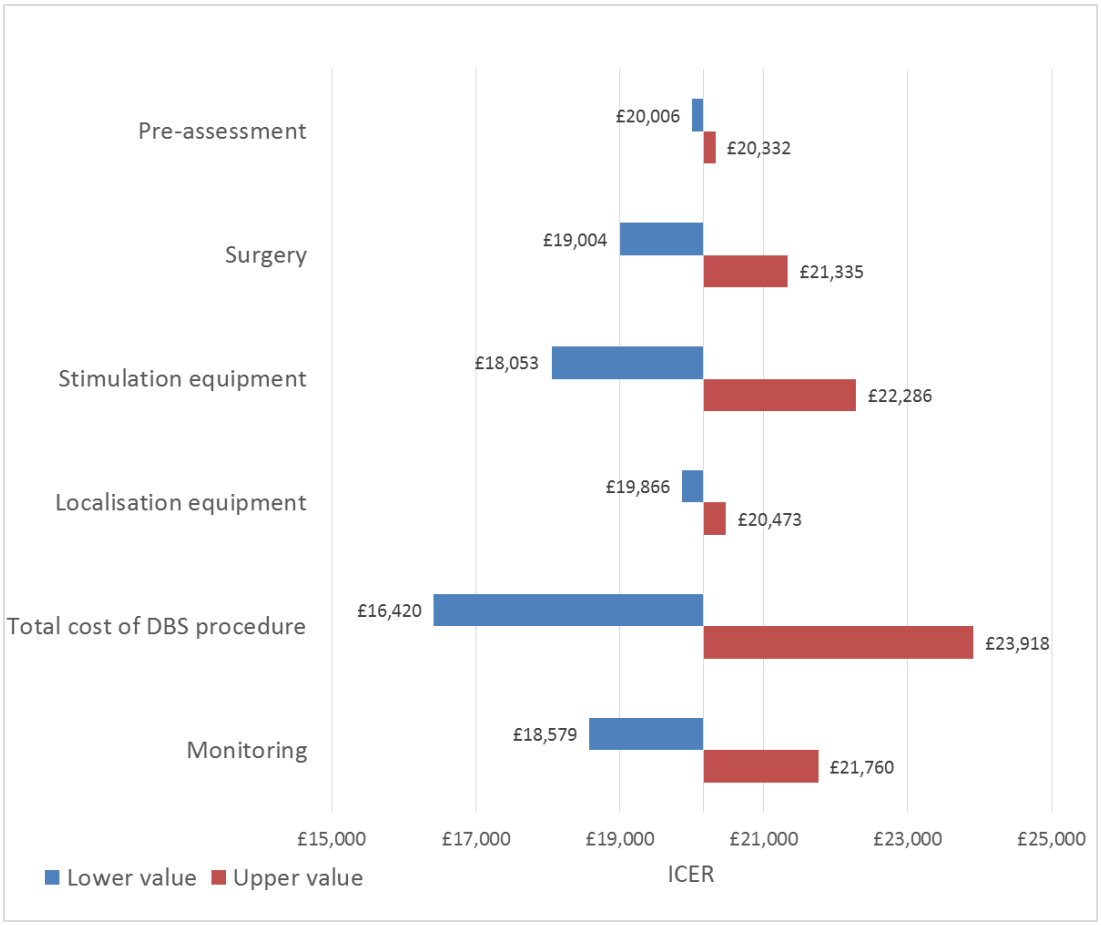


Figure 4: Tornado diagram of the costs to treat the complications of DBS (Romito 2015))

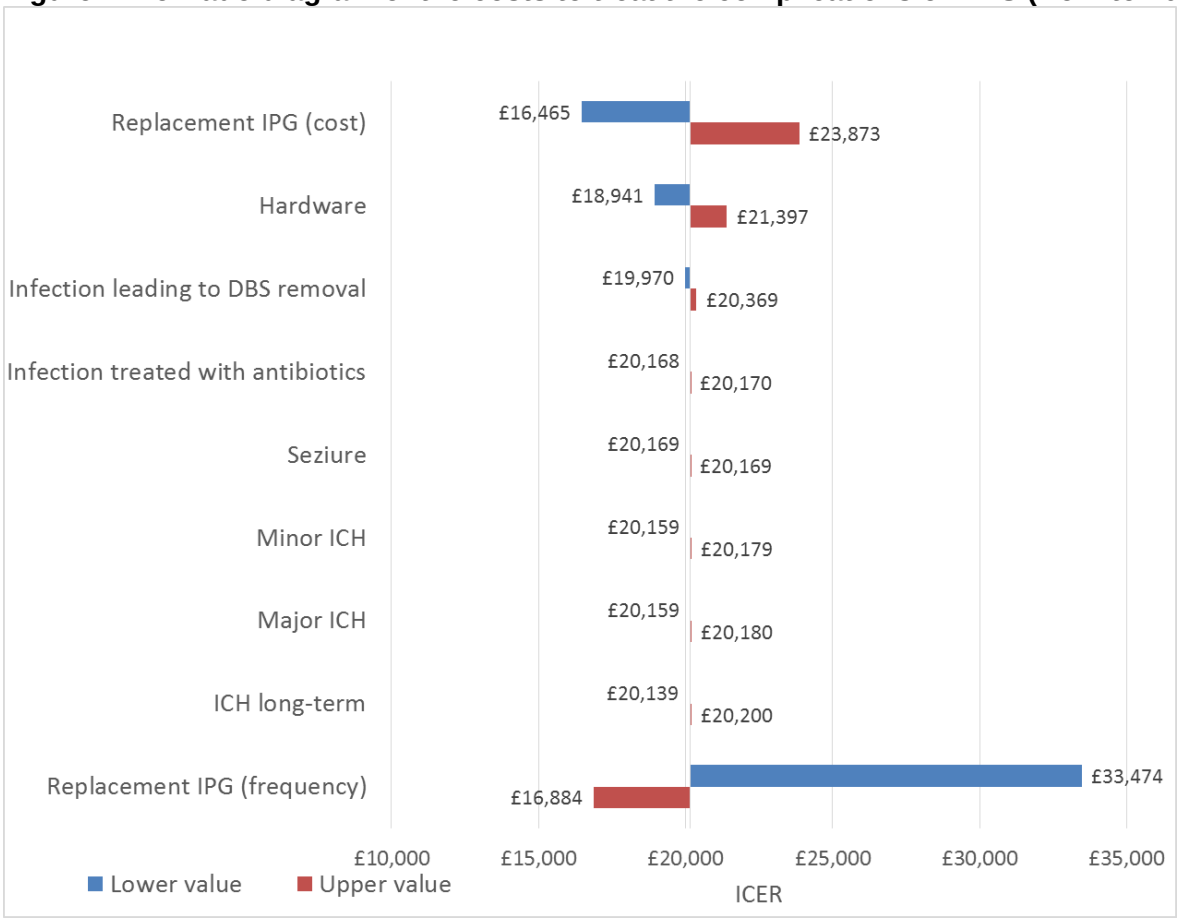


Figure 5: Tornado diagram of the costs associated with the procedure and monitoring (Viadilhet 2009)

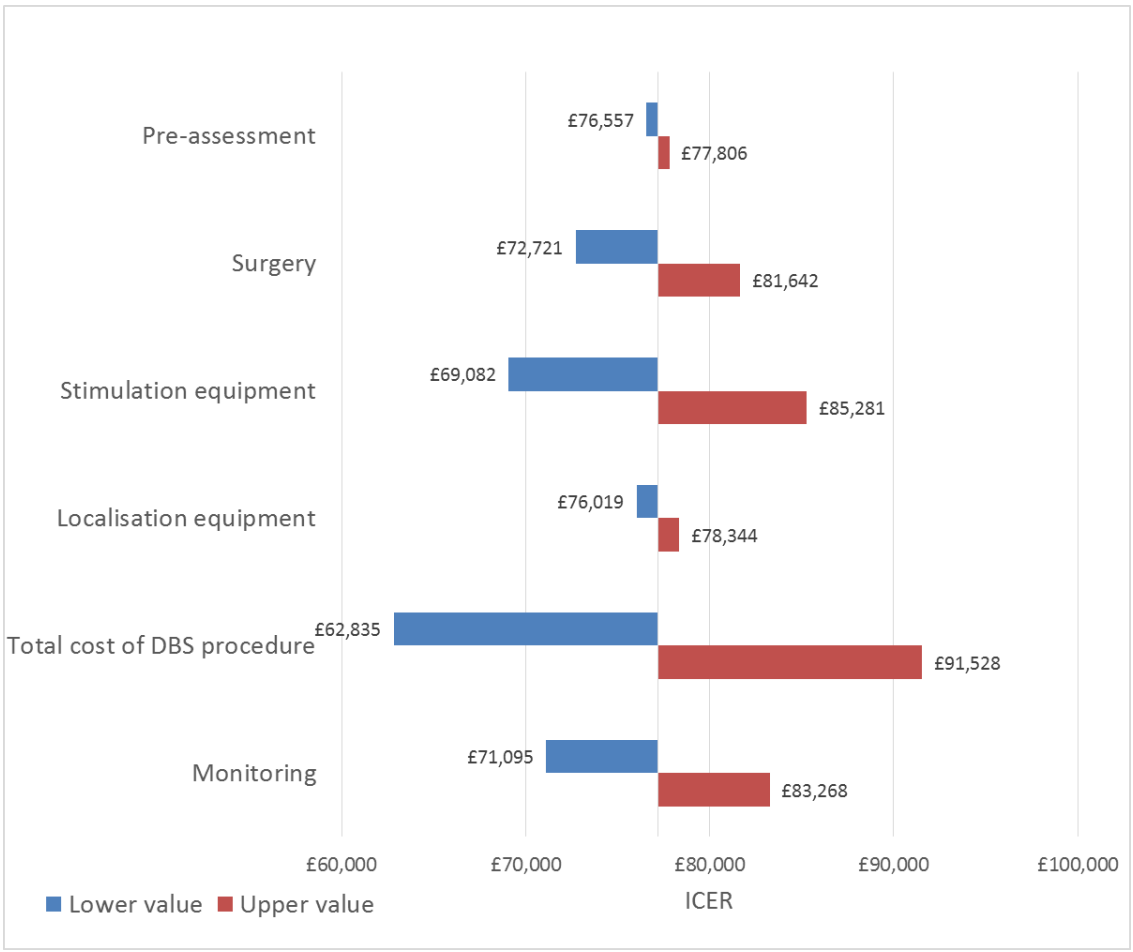
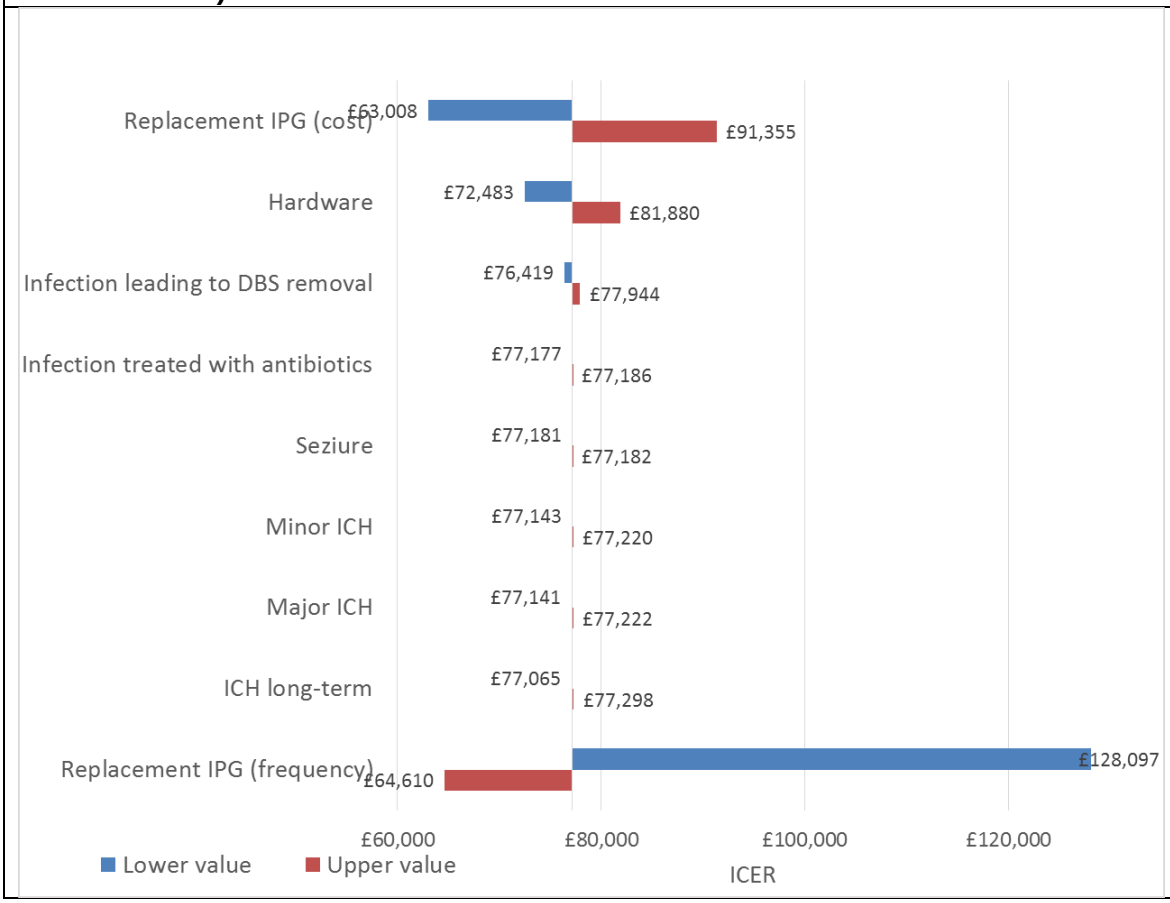

Pre-assessment
£76,557
£77,806
Surgery
£72,721
£81,642
Stimulation equipment
£69,082
£85,281
Localisation equipment
£76,019
£78,344
Total cost of DBS procedure
£62,835
£91,528
Monitoring
£71,095
£83,268
£60,000
£70,000
£80,000
£90,000
£100,000
ICER
Lower value
Upper value

Figure 6: Tornado diagram of the costs to treat the complications of DBS (Vidailhet 2009)



Probabilistic results

For Romito 2015, all simulations found DBS to be more effective and more expensive than usual care with a mean probabilistic ICER of £20,077. Furthermore, 739 of 1,000 simulations had ICER's below £20,000 and 927 below £30,000. This is illustrated in Figure 3 where simulations cross the £20,000 threshold in the north-east quadrant. The cost effectiveness acceptability curve (CEAC) also illustrated that DBS would be considered as the most optimal treatment for any threshold over £17,000 per QALY (Figure 8). In Figure 3 the simulations do not fall below an incremental cost of £60,000 the cost to provide DBS.

Figure 7: PSA simulations (Romito 2015)

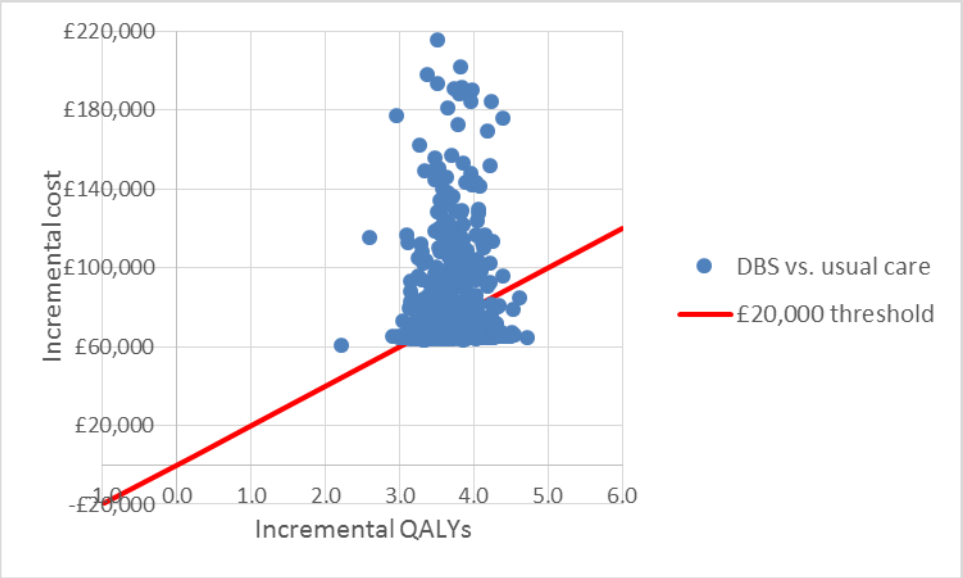
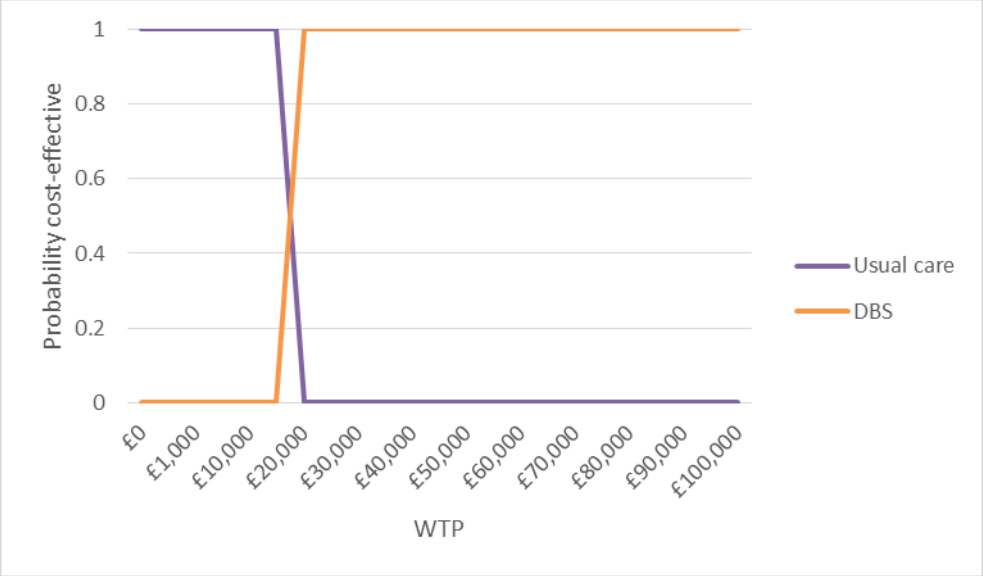
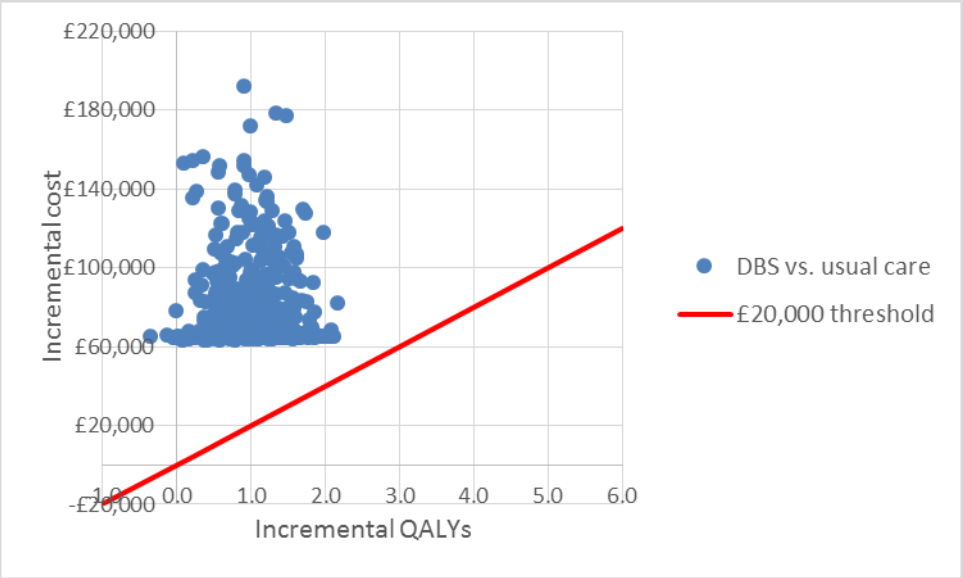


Figure 8: CEAC (Romito 2015)



When Vidailhet 2009 was used to inform the model, the mean ICER was £72,323 with almost all simulations (996 of 1,000) in the north-east quadrant above NICE's threshold (Figure 9). The CEAC also illustrated that usual care would be considered as the most optimal treatment for thresholds up to £65,000 per QALY (Figure 8).

Figure 9: PSA simulations (Vidailhet 2009)



Conclusions

DBS is more effective but also more costly than usual care when either study is used to inform the model. When the ICER is considered, DBS could be considered cost effective according to Romito 2015, who produce an ICER just above NICE's advisory threshold of £20,000 per QALY in the base case with many iterations of the PSA being below it. The opposite was the case when Vidailhet was used to inform the model with both the base case and nearly all iterations of the PSA, DBS was above NICE's conventionally held threshold of £20,000 per QALY and therefore not considered cost effective.

Given the large uncertainty inherent in the clinical evidence it is difficult to make strong conclusions. Greater certainty around cost effectiveness would be obtained through further research. Given the evidence around cost effectiveness DBS should only be considered for use when all other medical and surgical interventions have been considered and exhausted – in line with the current NHS commissioning policy on DBS for dystonia. Resource impact

Pharmacological treatments

According to NHS Reference Costs 2015/16 the first attendance for a pre-assessment in neurology would cost £217 (currency code WF01B, service code 400, non-admitted face-to-face attendance, first, neurology), but the committee advised that pharmacological treatments for dystonia could be initiated by a specialist clinic neurologist, rehabilitation medicine consultant, specialist nurse or specialist prescribing physiotherapist.

Drug acquisition costs for all pharmacological interventions for which evidence was searched, were taken from the NHS Electronic Drug Tariff May 2017, unless otherwise stated.(Table 11) Dosages in the BNF 75 were verified with the committee to ensure the dosages were appropriate for this patient group.

Table 11: Drug acquisition cost

Treatment	Pack size	Basic price	Price per unit
Tetrabenazine [a]			
Tetrabenazine 25mg tablets	112	£100.00	£0.89
Trihexyphenidyl [b]			

Treatment	Pack size	Basic price	Price per unit
Trihexyphenidyl 2mg tablets	84	£4.40	£0.05
Trihexyphenidyl 5mg tablets	84	£17.91	£0.21
Trihexyphenidyl 5mg/5ml oral solution	200	£22	£0.55/ 5ml
Gabapentin [c]			
Gabapentin 100mg capsules	100	£1.79	£0.02
Gabapentin 300mg capsules	100	£2.60	£0.03
Gabapentin 400mg capsules	100	£3.01	£0.03
Gabapentin 50mg/ml oral solution sugar free	150	£69.00	£0.46/ 1ml
Gabapentin 600mg tablets	100	£7.45	£0.07
Gabapentin 800mg tablets	100	£29.47	£0.29
Pregabalin [d]			
Pregabalin 100mg capsules	84	£96.60	£1.15
Pregabalin 150mg capsules	56	£64.40	£1.15
Pregabalin 200mg capsules	84	£96.60	£1.15
Pregabalin 20mg/ml oral solution sugar free	473	£99.48	£0.21/ 1ml
Pregabalin 225mg capsules	56	£64.40	£1.15
Pregabalin 25mg capsules	56	£64.40	£1.15
Pregabalin 300mg capsules	56	£64.40	£1.15
Pregabalin 50mg capsules	84	£96.60	£1.15
Pregabalin 75mg capsules	56	£64.40	£1.15
Levodopa [e]			
Levodopa 100mg / Carbidopa 25mg / Entacapone 200mg tablets	30	£20.79	£0.69
Levodopa 100mg / Carbidopa 25mg / Entacapone 200mg tablets	100	£69.31	£0.69
Levodopa 125mg / Carbidopa 31.25mg / Entacapone 200mg tablets	30	£20.79	£0.69
Levodopa 125mg / Carbidopa 31.25mg / Entacapone 200mg tablets	100	£69.31	£0.69
Levodopa 150mg / Carbidopa 37.5mg / Entacapone 200mg tablets	30	£20.79	£0.69
Levodopa 150mg / Carbidopa 37.5mg / Entacapone 200mg tablets	100	£69.31	£0.69
Levodopa 175mg / Carbidopa 43.75mg / Entacapone 200mg tablets	30	£20.79	£0.69
Levodopa 175mg / Carbidopa 43.75mg / Entacapone 200mg tablets	100	£69.31	£0.69
Levodopa 200mg / Carbidopa 50mg / Entacapone 200mg tablets	30	£20.79	£0.69
Levodopa 200mg / Carbidopa 50mg / Entacapone 200mg tablets	100	£69.31	£0.69
Levodopa 50mg / Carbidopa 12.5mg / Entacapone 200mg tablets	30	£20.79	£0.69
Levodopa 50mg / Carbidopa 12.5mg / Entacapone 200mg tablets	100	£69.31	£0.69
Levodopa 75mg / Carbidopa 18.75mg / Entacapone 200mg tablets	30	£20.79	£0.69
Levodopa 75mg / Carbidopa 18.75mg / Entacapone 200mg tablets	100	£69.31	£0.69

Treatment	Pack size	Basic price	Price per unit
Botulinium toxin type A [f]			
Botox 50unit powder for solution for injection vials (Allergan Ltd)	1	£77.50	£77.50
Xeomin 50unit powder for solution for injection vials (Merz Pharma UK Ltd)	1	£72.00	£72.00
Botox 100unit powder for solution for injection vials (Allergan Ltd)	1	£138.20	£138.20
Xeomin 100unit powder for solution for injection vials (Merz Pharma UK Ltd)	1	£129.90	£129.90
Botox 200unit powder for solution for injection vials (Allergan Ltd)	1	£276.40	£276.40
Xeomin 200unit powder for solution for injection vials (Merz Pharma UK Ltd)	1	£259.80	£259.80
Dysport 300unit powder for solution for injection vials (Ipsen Ltd)	1	£92.40	£92.40
Dysport 500unit powder for solution for injection vials (Ipsen Ltd)	2	£308.00	£154.00

(a) Tetrabenazine BNF: Movement disorders due to Huntington's chorea, hemiballismus, senile chorea, and related neurological conditions. By mouth, adult: Initially 25 mg 3 times a day, then increased, if tolerated, in steps of 25 mg every 3–4 days; maximum 200 mg per day.

(b) Trihexyphenidyl is not currently licensed for use in cerebral palsy. GC advise 1mg a day increasing up to 4mg three times a day, maximum 20mg per day.

(c) Gabapentin is not currently licensed for use in cerebral palsy. The committee advise dosage for that of focal seizures. BNF: Monotherapy for focal seizures with or without secondary generalisation. By mouth, adult: Initially 300 mg once daily on day 1, then 300 mg twice daily on day 2, then 300 mg 3 times a day on day 3, alternatively initially 300 mg 3 times a day on day 1, then increased in steps of 300 mg every 2–3 days in 3 divided doses, adjusted according to response; usual dose 0.9–3.6 g daily in 3 divided doses

(d) Pregabalin is not currently licensed for use in cerebral palsy. The committee advise dosage for that of focal seizures. BNF: Adjunctive therapy for focal seizures with or without secondary generalisation. By mouth, adult: initially 25 mg twice daily, then increased in steps of 50 mg daily, dose to be increased at 7 day intervals, increased to 300 mg daily in 2–3 divided doses for 7 days, then increased if necessary up to 600 mg daily in 2–3 divided doses.

(e) Levodopa is not currently licensed for use in cerebral palsy. GC advise 3 to 10 tablets per day.

(f) NHS indicative price taken from the BNF

Often, oral treatments for dystonia do not incur administration costs as they are administered at home, without health care professional assistance. However, if families or carers administer oral treatments via PEG, they will require additional training and equipment. Oral treatments may be monitored by the patient's GP and community team at routine visits, but advice from a rehabilitation medicine or neurologist on increasing or decreasing medication would be sought if they were not directly responsible for monitoring the treatment. Furthermore, for levodopa, an additional review with the patient's GP or neurologist after the initial 3 months of treatment would be incurred to assess efficacy.

Botulinum toxin involves a day–case admission performed by a neurologist, rehabilitation medicine doctor, or a specially trained physiotherapist or nurse in a specialist clinic. Adults with cerebral palsy are unlikely to be sedated, but ultrasound or electromyography (EMG) may be used for guidance.

The appointment for the injection of botulinum has a NHS reference cost assigned – Torsion dystonia and other involuntary movements drugs band 1 (code XD09Z). This reference cost (£324) will include all costs related to the procedure, the day case admission, drug costs and staff costs.

Following the injections, patients would be monitored every 3 to 4 months by the specialist clinic at a cost of £161 (NHS Reference Costs 2015/16, currency code WF01A, service code 400, non-admitted face-to-face attendance follow-up, neurology) to assess their response and need for repeat injections.

Dynamic orthotics

Healthcare Improvement Scotland identified no published cost-effectiveness evidence on dynamic lycra splinting. For completeness they provided the cost of body suits currently available from personal communications. Those costs are presented alongside costs converted to 2015/16 using the hospital and community health services pay and prices index uplift (Curtis 2015) in Table 12.

Table 12: Cost of dynamic orthotic equipment

Orthotic equipment	2011/12 prices	2015/16 prices
Lycra® body suit	£2,130	£2,239
Upper limb splint from Second Skin	£1,495	£1,572
Vest with sleeves costs from DM Orthotics	£357	£375
Vest with sleeves costs from Jobskin	£383	£403
Suit from DM Orthotics	£485	£510
Suit from Jobskin	£509	£535

(a) HSHC inflations factor 1.0513 (2015/16 PPI 297/ 2011/12 PPI 282.5

Dynamic orthotic equipment would be offered after an assessment with an orthotist (NHS Reference Costs 2015/16 WF01B 658, £77) following a referral from an occupational therapist or physiotherapist. Orthotic equipment should be reviewed annually by an occupational therapist (regarding upper limb and hand orthotics), physiotherapist (regarding body suits or legs and feet orthotics) or orthotist. If there is a 'change' or ‘problem’ 2 or 3 of those healthcare professional may complete a joint review (Table 13).

Table 13: Follow-up costs, orthotics

HCP conducting review	Cost per attendance	Source
Occupational therapist	£58	NHSRC 2015/16 WF01A 651
Physiotherapist	£46	NHSRC 2015/16 WF01A 650
Orthotics	£62	NHSRC 2015/16 WF01A 658

NHSRC: National Health Systems Resource Centre

The committee advised that orthotic equipment would typically last between 6 to 24 months before it needs to be replaced, but reiterated that the lifespan would depend on how much it is used and during which activities.

Intrathecal baclofen (ITB)

Sampson 2002 published a study on ITB in which detailed cost estimates were derived from 3 centres in the UK where the procedure was being performed. The costs included in the study were obtained in 1999 and have been converted to 2015/16 costs using the hospital and community health services pay and prices index uplift (Curtis 2015) in Table 14.

Table 14: Cost of intrathecal baclofen reproduced from Sampson 2002

Resource use	1999 prices (mean)	Mean 2015/16 prices [a]
Pre-screening assessment costs (30 minutes neurosurgeon time and outpatient clinic visit)	£330 to £556 (£443)	£698
Test dose (Lumbar puncture, lumbar catheter, injection of a therapeutic substance, 2 days hospitalisation, drug costs, physiotherapist, and nursing time for patient observation)	£940 to £1,570 (£1,255)	£1,976
Cost of implantation procedure (cost of pump,	£8,730 to £10,260	£14,952

Resource use	1999 prices (mean)	Mean 2015/16 prices [a]
catheter, procedure, drugs, 5-day inpatient stay)	(£9,495)	
Other costs (tests, pathology, radiology, microbiology), excluding potential transport	£550	£866
Total cost of procedure	**£11,743**	**£18,492**
Cost of follow-up (refill kit, drug costs, physiotherapist assessment, and outpatient visit) with an average of 4 to 8 refills per year	£140 to £150 per refill £145 x 6 refills per year = £870 annual cost	£1,370
Discounted follow-up over 5 years	£3,677	£5,790
Total discounted cost over 5 years	**£15,420**	**£24,283**

(a) HSHC inflation factor 1.5748 (2015/16 PPI 297/ 1999/2000 PPI 188.6)

The East Midlands Specialised Commissioning Group also produced detailed paediatric and adult costs for ITB treatment in 2009. They assumed the admission for the test dose usually takes 2 days whilst the admission for the implant usually takes an additional 5 days. The test dose, implant and refills were worked out using the contract code AB05Z (for intermediate pain procedures), at 2009/2010 prices. Those prices are presented alongside 2015/16 costs in Table 15.

Table 15: Cost of ITB treatment based on East Midlands commissioning policy 2009

Resource use	Adult cost, 2009/10 prices	2015/16 prices [a]
Test dose	£680	£752
Implant procedure	£515	£569
Device and catheters	£9,446	£10,445
Total cost of procedure	**£10,641**	**£11,766**
Annual cost of refills (assuming 4 per year)	£2,130	£2,355
Total cost of procedure and follow-up in first year	£12,771	£14,121
Discounted follow-up appointments over 4 further years	£7,685	£8,497
Total discounted cost over 5 years	**£20,456**	**£22,618**

(a) HSHC inflation factor 1.1057 (2015/16 PPI 297/ 2009/10 PPI 268.6)

The total costs over 5 years are similar in the Sampson 2002 study and in the East Midlands Commissioning Policy; however, it is likely that the costs from the latter source are more accurate as costs were based on an HRG code, reflecting more recent UK practice.

Evidence statements

Comparison 1: Levodopa versus placebo

Critical outcomes

Health related quality of life

- No evidence was found for this outcome.

Dystonia

- No evidence was found for this outcome.

Patient or carer reported satisfaction

- No evidence was found for this outcome.

Important outcomes

Motor function using functional measures

- Low quality evidence from 1 randomised trial including 9 people with cerebral palsy and dystonia suggested no clinically important effect of levodopa as compared to placebo on motor function assessed using the QUEST score.

Goal attainment scores

- No evidence was found for this outcome.

Adverse events

- Very low quality evidence from 1 randomised trial including 9 people with cerebral palsy and dystonia identified no adverse effects associated with levodopa.

Pain

- No evidence was found for this outcome.

Comparison 2: bilateral pallidal deep brain stimulation (DBS) – pre versus post-operative

Critical outcomes

Health related quality of life

- Very low quality evidence from 2 before and after studies of DBS in 28 people with cerebral palsy and dystonia indicated a clinically important improvement in some of the subscales of the SF-36 health related quality of life measure following DBS.

Dystonia

- Very low quality evidence from 4 before and after studies of bilateral pallidal deep brain stimulation (DBS) in 42 people with cerebral palsy and dystonia indicated a clinically important reduction in dystonia following DBS.

Patient or carer reported satisfaction

- No evidence was found for this outcome.

Important outcomes

Motor function using functional measures

- No evidence was found for this outcome.

Goal attainment scores

- No evidence was found for this outcome.

Adverse events

- Very low quality evidence about adverse events following DBS came from 2 before and after studies of DBS in 28 people with cerebral palsy and dystonia. Adverse events included: hypophonia, dysarthria, localised pain, paraesthesia, anxiety, requirement to adjust the stimulator due to ineffectiveness and stimulator failure following exposure to magnetic field.

Pain

- Very low quality evidence from 1 before and after study of DBS in 13 people with cerebral palsy and dystonia indicated no clinically important reduction in pain following DBS.

Recommendations

A3.1 When considering any treatments for spasticity or dystonia, discuss with the adults with cerebral palsy (and their families and carers, if agreed):

- treatment goals (and document them) **and**
- the benefits and risks of treatments (for example, the risk of deterioration in function) as part of their multidisciplinary treatment strategy.

For further information on supporting people to actively participate in their care and shared decision-making see NICE's guideline on patient experience in adult NHS services.

A3.2 Be aware that adults with cerebral palsy may have both spasticity and dystonia. The severity of symptoms for both conditions may fluctuate in response to health, social and environmental factors.

A3.3 At every review, discuss with the person with cerebral palsy (and their families and carers, if agreed) factors that may exacerbate their spasticity or dystonia, such as:

- bladder problems (for example, urinary tract infection or bladder stones)
- constipation
- emotional distress
- pain
- posture
- pressure sores
- changes in home or work environments, including seating
- medication changes and side effects.

A3.4 Address any modifiable factors identified that may be exacerbating spasticity or dystonia before discussing further management options with the adult with cerebral palsy.

A3.5 Discuss with the person with cerebral palsy (and their families and carers, if agreed) the balance between benefits and harms of treating spasticity and dystonia. In particular, explain that some people use their spasticity or dystonia to help their posture and ability to stand, walk or transfer, and that treatment may affect this.

A3.6 Refer adults with cerebral palsy and problematic dystonia (for example, causing problems with function, pain or participation) to a tone or spasticity management service to consider treatment options.

A3.7 Do not prescribe levodopa[a] to manage dystonia in adults with cerebral palsy, except in the rare situation when it is used for a therapeutic trial in dopa-responsive dystonia.

A3.8 Do not rapidly withdraw enteral[b] drugs for treating dystonia if the person has been taking them for more than a few weeks. Reduce the dosage gradually to avoid withdrawal symptoms.

[a] At the time of consultation (July 2018), levodopa did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[b] At the time of consultation (July 2018) oral formulations are usually not licensed to be given via an enteral feeding tube so administration via this route would be off-label. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

A3.9 Only consider botulinum toxin type A[c] treatment for focal dystonia in adults with cerebral palsy when:

- the person is under the supervision of a tone or spasticity management service, and it is part of a wider programme of therapy **and**
- local dystonia is:
  - affecting their care (such as hygiene or dressing), **or**
  - causing pain **or**
  - impairing activity and participation.

A3.10 When considering botulinum toxin type A[c] treatment, take into account and explain to the adult with cerebral palsy (and their family and carers, if agreed):

- that the severity and pattern of dystonia may change following treatment **and**
- the potential impact of treatment on function.

A3.11 Only consider continuous pump-administered intrathecal baclofen[d] if people with cerebral palsy still have difficulties with dystonia, despite having enteral anti-dystonic drug treatment or botulinum toxin type A7 treatment. Provide information and discuss the procedure, including intrathecal baclofen testing, with the person (and their family or carer, if agreed) as described in recommendations A2.2 to A2.5.

A3.12 1.3.25 If adults with cerebral palsy continue to have severe and painful dystonia, despite having enteral anti-dystonic drug treatment or botulinum toxin type A treatment, consider referring them to a specialised centre with experience in providing deep brain stimulation. See also NICE interventional procedure guidance on deep brain stimulation for tremor and dystonia (excluding Parkinson's disease).

Rationale and impact

Why the committee made the recommendations

Initial management of spasticity and dystonia

The committee noted that there is a lack of understanding about the relationship between spasticity and dystonia. Based on their experience, they agreed that a better understanding of these conditions and the factors that affect them is likely to lead to more effective decisions about management. They discussed factors that commonly trigger or worsen symptoms of both spasticity and dystonia, and their concerns that these may sometimes go unrecognised.

The committee also discussed the balance of benefits and risks of treatment to reduce spasticity and dystonia. In particular, some people with cerebral palsy make functional use of their increased muscle tone from spasticity and dystonia, for example to help them walk or transfer independently. For these people a reduction in spasticity or dystonia could have a negative impact on function. To ensure informed decision-making, the risks and benefits of treatment should be discussed with each person and specific treatment goals should be agreed.

[c] At the time of consultation (July 2018), botulinum toxin type A did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[d] Although intrathecal baclofen is licensed in UK clinical practice for severe spasticity, at the time of consultation (July 2018) it did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

There was limited evidence on treatments for spasticity and dystonia in adults with cerebral palsy, but based on their experience and expertise the committee agreed on a stepwise approach to treatment dependant on tolerability and effectiveness:

- first identifying and managing any factors that might be exacerbating their symptoms and considering a physical management programme
- next considering enteral (oral or via a feeding tube) drug treatment and referral
- then considering more invasive options.

There was limited evidence on treating dystonia in adults with cerebral palsy. The committee discussed that it is a specialist clinical area and that the benefits and harms of treatments would need to be assessed by a person with expertise in tone management. Therefore, the committee agreed that adults with cerebral palsy should be referred for specialist management if they have problematic dystonia.

Drug treatment

Enteral anti-dystonic drug treatment

The evidence for levodopa was limited, although there was some evidence that it was not effective for reducing dystonia in adults with severe impairment. Taking into account the lack of evidence of effectiveness, and also the potential for side effects and the cost of long-term treatment to the NHS, the committee agreed that levodopa should not be prescribed routinely for dystonia in adults with cerebral palsy. However, the committee agreed that a trial of levodopa can be useful to exclude the rare but treatable condition of dopa-responsive dystonia.

No evidence was identified for other enteral anti-dystonic drug treatments. However, based on their experience of current practice, the committee acknowledged that there are enteral drug treatments available that might be beneficial for some people. They agreed that first-line treatment options should depend on the person's symptoms and treatment goals, and should only be considered by a specialist service.

Botulinum toxin type A

No evidence was identified on using botulinum toxin type A injections for treating dystonia in adults with cerebral palsy. However, based on their knowledge and experience, the committee agreed that it can be of benefit to some people with focal dystonia. Because there was no evidence and this treatment is more invasive and costly than other enteral anti-dystonic drug treatments, the committee agreed that it should only be considered under specialist supervision for people with focal dystonia and difficulties with symptoms, who might gain the most benefit from the treatment. They also agreed that it should only be used as part of a programme of therapy. This would usually involve a physical management programme, for example, including physiotherapy and splinting.

The committee emphasised that botulinum toxin type A injections should be given by an experienced specialist. This is important because the injections need to be accurately placed for successful treatment and to avoid side effects.

Neurosurgical treatment

Intrathecal baclofen

Despite a lack of evidence, the committee agreed that their knowledge and experience of current practice supported the use of intrathecal baclofen pumps for treating dystonia in some adults with cerebral palsy. However, they should only be considered by a specialist service that can safely carry out the procedure and has the expertise to assess whether it is

a suitable treatment for the person. There are potential risks of intrathecal baclofen pump treatment. these include infections, catheter breakage, seizures, constipation and anxiety or depression. It is also more costly than other drug treatments. Taking into account these factors, the committee agreed that it should only be considered when a person still has difficulties with dystonia after trying enteral anti-dystonic drug treatment or botulinum toxin type A injections.

The committee also highlighted the importance of discussing the procedure with the person and their family or carer, so that they fully understand what the treatment involves and the potential risks and benefits.

The committee agreed that the same considerations about intrathecal baclofen testing that have been made for spasticity also apply to dystonia and therefore cross referenced to the relevant recommendations.

Deep brain stimulation

Although there was limited and sometimes incongruous evidence for deep brain stimulation, it did suggest some improvement in dystonia after treatment. However, some complications were noted, including problems with speech, pain, numbness and anxiety, as well as problems with the equipment. Deep brain stimulation is expensive. Two studies identified as part economic evidence, suggested it would improve quality of life. However, the economic evidence was inconsistent, showing that it was likely to be cost effective in people with dystonia that has not improved with other treatments when based on the outcomes of one quality of life study but not cost effective using the other. The committee also took into account NICE's interventional procedures guidance on deep brain stimulation for tremor and dystonia (excluding Parkinson's disease) published in 2006, which supports its use with the involvement of a multidisciplinary team. Based on the evidence on improvements in quality of life and the committee's knowledge and experience, they agreed that deep brain stimulation should only be considered for people who have severe and painful dystonia, and only carried out at an experienced specialised centre.

Impact of the recommendations on practice

Overall, the recommendations reflect current good practice and will help to eliminate variation, particularly in referral. There may be a change to practice because levodopa will no longer be prescribed routinely, and this may result in a small cost saving.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The critical outcomes for consideration in dystonia were health related quality of life and patient satisfaction. These were prioritised due to the disruptive effect of uncontrolled muscle spasms on daily life. Motor function, reduction of pain, goal attainment and treatment related adverse events were important outcomes. Health related quality of life was reported in studies that assessed the effectiveness of deep brain stimulation. However, in the trial on levodopa only change in motor function and adverse events were reported. No evidence was found for other potential antidystonic pharmacological treatments such as trihexyphenidyl, botulinum toxin injections, gabapentin/ pregabalin, tetrabenazine, intrathecal baclofen; or orthotic use to improve physical function for dystonia in adults with cerebral palsy (such as Lycra garments).

The quality of the evidence

Evidence for outcomes comparing treatments was very low to low quality according to GRADE and was only available for levodopa compared to placebo and for pre-postoperative comparison of deep brain stimulation.

The evidence had several limitations. The trial on levodopa included people with dystonia related to cerebral palsy who were quadriplegic with GMFCS ranging from III to V. This means that they were severely impaired and is the committee therefore noted that the results of this trial could not be generalised to all people with cerebral palsy who have dystonia.

Study design was also a factor that lowered the committee's confidence in the evidence. The evidence to assess the effectiveness of deep brain stimulation came from before and after observational studies. It was often not clearly described what kinds of treatments people have had prior to having deep brain stimulation and it is also not clear whether the benefits or risks would have been the same or different to any other type of intervention since there was no comparison group.

Benefits and harms

Based on their experience the committee discussed that the relationship between spasticity and dystonia is not always clear to healthcare professionals and that better knowledge of this would lead to more effective shared decision. To highlight the complexity of conditions of abnormal muscle tone they therefore decided to describe that adults with cerebral palsy can have both spasticity as well as dystonia and that symptom severity may vary.

The committee, based on their experience and expertise, agreed that there are a number of factors that can contribute to, or exacerbate, both spasticity and dystonia. They highlighted those factors that are most commonly associated with spasticity or dystonia and that are not always recognised as such. Identifying and addressing these improves the effectiveness of any multidisciplinary spasticity treatment strategy by focusing the management plan (for example if dystonia is exacerbated by pressure sores or constipation then a treatment plan should address these factors first).

Based on their experience and expertise the committee considered that treatment of both spasticity and dystonia can reduce pain and improve sleep, has an impact on motor function and can improve quality of life. The difference between spasticity, voluntary resistance and contractures requires careful assessment and it may not be possible to tell them apart in one assessment, or until treatment is initiated where movement is severely restricted. The committee discussed that spasticity as well as dystonia can have a positive impact on motor function. Some people with cerebral palsy make functional use of their increased muscle tone from spasticity and dystonia, for example to help them walk. For these people reduction in spasticity or dystonia could have a negative impact on certain motor functions, for example loss of their ability to transfer independently. However, severe spasticity can also have a negative impact on motor function as increased muscle tone can limit function.

The committee agreed that the risks and benefits should be discussed with each person before treatment and specific treatment goals are agreed. In relation to potentially positive or negative effects of increased tone, the committee highlighted that goals need to be clearly set out and that this should also feature in multidisciplinary team discussions to assess potential changes in function. This would also lead to better shared decision making and would inform the assessment of whether or not treatments are effective.

Apart from limited evidence related to levondopa and bilateral pallidal deep brain stimulation there was no evidence identified for other medicines or neurosurgical procedures. The committee noted that that it is a specialist clinical area. Based on their experience they acknowledged that there are enteral drug treatments available (such as trihexyphenidyl and

gabapentin) that might be beneficial for some people. To balance the benefits and harms of these, and other more invasive options they agreed that treatments should only be considered by a specialist service and would depend on the person's symptoms and treatment goals. Therefore, the committee agreed that adults with cerebral palsy should be referred for specialist management if they have problematic dystonia.

There was some evidence that levodopa was not effective in adults with cerebral palsy and dystonia and severe impairment. Due to the lack of evidence for effectiveness, the potential for side effects the committee agreed that levodopa should not be prescribed routinely for dystonia in cerebral palsy. However, they decided that a trial of levodopa can be useful to exclude the rate, but treatable, condition of dopa-responsive dystonia.

Based on their expertise and experience the committee noted that stopping antidystonic drugs too quickly could lead to severe symptoms (for example anxiety and panic attacks) particularly if it has been taken for a few weeks. Therefore they agreed that the dose of the medication should be gradually reduced before stopping it to minimise risk.

The committee made a recommendation, based on experience and knowledge, for the use of botulinum toxin type A as a treatment for focal dystonia, particularly when it is causing pain and is affecting their care or function. They recommended such treatment should be supervised by a tone or spasticity management service because expert assessment and a wider management programme (that may include physiotherapy and splinting) is also needed to get optimise the benefit of the treatment.

The committee noted, based on their experience and expertise that focal interventions in some individuals with dystonia and cerebral palsy may alter the balance of motor function, adversely affecting the outcomes. The committee acknowledged this and recommended it should be taken into account during consideration of botulinum toxin type A therapy.

No evidence was identified for the use of continuous pump administered intrathecal baclofen. Given the risks associated with this surgical procedure the committee decided that this should only be considered when all other options have been exhausted. They agreed that the specific benefits and harms of this procedure should be discussed and as well as the test dose and how to assess the response with the adults with cerebral palsy (and their family or carer, if appropriate) and therefore cross referred to the relevant recommendations in the section on neurosurgical treatments to reduce spasticity (A2.2 to A2.5).

Although there was limited evidence for deep brain stimulation, it did suggest some improvement in dystonia after treatment. However, some serious complications were noted, including problems with speech, pain, numbness and anxiety, as well as problems with the equipment. The committee therefore agreed that this should only be considered after referral to a specialist centre with experience in providing this procedure. The committee acknowledged that there are not many of these centres who provide this, but agreed that there would only be a small proportion of adults with cerebral palsy who may benefit from this.

Cost effectiveness and resource use

The committee noted that no relevant published economic evaluations had been identified for this topic.

Dystonia is aggravated by factors such as pain and anxiety which if not identified and managed appropriately, can negatively impact on the patients' health-related quality of life. Therefore, knowing what factors can aggravate dystonia may lead to increased vigilance and thus more timely management with potential cost savings. Estimating the costs to manage those factors would go beyond the scope of the guideline although they were likely to offset the cost of the recommendations.

The committee discussed the evidence that levodopa provided no additional benefit compared to placebo and agreed that relatively cheap treatments should not be recommended if they are ineffective or have the potential to incur adverse effects. For this reason, the committee made a recommendation to not routinely prescribe levodopa to stop potentially cost-ineffective practices. However, other pharmacological treatments such as gabapentin and trihexyphendyl are currently available in practice and could be considered before more costly and more invasive options. Given that no evidence was identified on those alternatives, the committee made a recommendation to refer adults with problematic dystonia to a specialist movement disorder or spasticity service to consider treatment in line with their experience and expertise. The committee noted that a recommendation to refer adults to a specialist tone management team would not increase current resource use as it would be beyond the remit of GPs to initiate treatments for dystonia in primary care. The committee also noted it would be cost-ineffective to refer people with asymptomatic or tolerable dystonia as treatment would not provide any additional benefits to justify the cost, burden, or potential adverse effects of treatment.

The committee noted that no one should remain on cheap, ineffective treatments as the burden of treatment and long-term cost, including the cost to manage their adverse events could be substantial. However, treatments for dystonia should be discontinued gradually, to minimise withdrawal symptoms such as anxiety and distress, as those symptoms would offset the cost of immediate discontinuation.

Some centres would consider splinting (including dynamic Lycra) following an assessment with occupational therapy, before more invasive treatments such as botulinum toxin or intrathecal baclofen are considered. However, the committee acknowledged the high cost to provide orthotic equipment and agreed there was no clinical evidence it provided a cost effective use of resources to implement its wider use. For this reason, the committee made a research recommendation to assess the clinical and cost effectiveness of splinting options.

The committee stated botulinum toxin was frequently used in current practice to manage focal dystonia when it is causing discomfort or affecting care or function and cannot be managed effectively using cheaper, less invasive treatments. The committee agreed it was important to state those criteria in their recommendation to prevent practises which were unlikely to be cost effective. However, in the absence of comparative high quality evidence, the committee did not make a strong recommendation.

The committee agreed intrathecal baclofen therapy was an expensive but successful option provided by specialists to manage dystonia when other options have been exhausted. The committee also added that additional research on its effectiveness in a population of adults with cerebral palsy would not change current practice unless it was shown to be harmful as the benefits have been shown to outweigh the costs in other populations. In the absence of published evidence on intrathecal baclofen therapy in adults with cerebral palsy, the committee made a recommendation based on their clinical experience and expertise which they considered to reinforce best practice.

Deep brain stimulation (DBS) is a relatively new and expensive treatment used to manage dystonia in England and Wales and is commissioned in the NHS for patients with generalised dystonia, status dystonicus, laryngeal dystonia and cervical dystonia if the criteria set out in the commissioning policy are met. However, the cost effectiveness of DBS had not been assessed in adults with cerebral palsy when that policy was produced.

Two studies included in the clinical evidence review provided SF-36 data, before and after deep brain stimulation treatment which enabled a cost utility analysis to be developed. The Committee stated that it was crucial the complications of deep brain stimulation were taken into consideration when making their recommendations, as they may outweigh the benefits deep brain stimulation can provide. As a result, the economic modelling was used by the Committee as one of many ways to assess those trade-offs.

The results of the model were sensitive to the study used to inform the improvement in utility as one study included participants with a much lower utility pre-DBS who saw a much greater improvement in their utility post-DBS. The committee agreed that DBS would only be considered when all pharmacological treatments had failed and for this reason placed more weight on the study who included participants with a lower utility value pre-DBS. The committee also noted that that study included more participants and was relatively up-to-date (Romito 2015 N=15 vs. Vidailhet 2009 N=13).

Uncertain parameters were varied in deterministic one-way sensitivity analyses to assess the robustness of the results. Those parameters included the cost of the procedure, inclusion and consequences of complications and frequency of battery replacements. The results of those analyses provided ICERs below or within NICE's advisory threshold for cost-effectiveness when parameters set out in Romito 2015 were used to inform the model, providing evidence that DBS could be a cost-effective option. Those results were also reiterated in probabilistic analysis with 739 of 1,000 simulations below an ICER of £20,000.

Based on the economic evidence and their clinical expertise, the committee agreed that deep brain stimulation should be recommended in line with the current NHS commissioning policy as a cost effective option. As a result, the committee made a recommendation to consider a referral to a specialised tone management service with experience in providing deep brain stimulation for adults with intractable dystonia that is severe and painful.

Other factors the committee took into account

The committee also took into account the recommendations made in the NICE interventional procedure guideline Deep brain stimulation for tremor and dystonia (excluding Parkinson's disease) IPG188 (2006). It is recommended in IPG188 that deep brain stimulation can be used provided that the normal arrangements are in place for consent, audit and clinical governance and only in the context of a multidisciplinary team specialising in the long-term care of patients with movement disorders. The committee therefore believed that the recommendation that they made aligns with IPG188 and made a cross-reference to it.

References

Koy 2014

Koy, A., Pauls, K. A., Flossdorf, P. Young adults with dyskinetic cerebral palsy improve subjectively on pallidal stimulation, but not in formal dystonia, gait, speech and swallowing testing, European Neurology, 72, 340-8, 2014

Marks 2011

Marks, W. A., Honeycutt, J., Acosta, F. Dystonia due to cerebral palsy responds to deep brain stimulation of the globus pallidus internus, Movement Disorders, 26, 1748-1751, 2011

Pozin 2014

Pozin, I., Bdolah-Abram, T., Ben-Pazi, H., Levodopa does not improve function in individuals with dystonic cerebral palsy, Journal of Child Neurology, 29, 534-7, 2014

Romito 2015

Romito, L. M., Zorzi, G., Marras, C. E. Pallidal stimulation for acquired dystonia due to cerebral palsy: beyond 5 years, European Journal of Neurology, 22, 426-e32, 2015

Vidailhet 2009

Vidailhet, M., Yelnik, J., Lagrange, C. Bilateral pallidal deep brain stimulation for the treatment of patients with dystonia-choreoathetosis cerebral palsy: a prospective pilot study, The Lancet Neurology, 8, 709-717, 2009

Appendices

Appendix A – Review protocols

Review protocol for review question A3: Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?

Table 16: Review protocol for interventions for dystonia

Field (based on PRISMA-P)	Content
Key area in the scope	A. Management of abnormal muscle tone in adults aged 19 and over with cerebral palsy, including spasticity and associated movement disorders such as dystonia.
Draft review question from the scope (to be deleted in the final version)	A3 Which treatments (for example, levodopa, anticholinergic drugs, and botulinum toxin injections) are most effective for managing dystonia in adults with cerebral palsy?
Actual review question	A3 Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?
Type of review question	Intervention
Objective of the review	The aim of this review is to determine the relative effectiveness of pharmacological treatments and neurosurgical procedures for managing dystonia in adults with cerebral palsy
Eligibility criteria – **population**/disease/condition/issue/domain	Adults aged 19 and over with predominantly dystonic cerebral palsy (Study median of age 18 years or more)
Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s)	Pharmacological: • Levodopa • Anticholinergic drugs (trihexyphenidyl) • Botulinum toxin injections with adjunct treatments such as lycra and splint casting • Botulinum toxin injections without adjunct treatments • Gabapentin/ pregabalin

Field (based on PRISMA-P)	Content
	• Tetrabenazine Non-pharmacological: • Deep brain stimulation • Intrathecal baclofen ITB • Orthotics for physical function (dynamithorthotics [lycra])
Eligibility criteria – **comparator(s)/**control or reference (gold) standard	• Each other • Placebo • Usual care

Outcomes and prioritisation	**Critical outcomes**
	• Health related quality of life
	• Dystonia rating scales
	  ○ DMFRS
	  ○ Fahn-Marsden Rating Scale
	• Patient or carer reported satisfaction
	Important outcomes
	• Motor function using functional measures
	• Goal attainment scores
	• Adverse events
	• Pain
	
	Minimally important differences
	• Goal Attainment Scale: 7 units
	• Modified Ashworth Scale: 1 unit
	• Quality of Upper Extremities Test: 5 units
	• ICF - Measure of Participation and Activities Screener: 2 units
	• Community Balance and Mobility Scale: 10 units

Field (based on PRISMA-P)	Content
	• Five Times Sit to Stand Test: 2.5 seconds • Seated Shot-Put: 40cm • Timed Up and Go: 5 seconds • Pain: 30% reduction – corresponding to “much improved” or “very much improved” on a global impression of change, or 2 points on a 0 to 11 pain intensity numerical rating scale • Other dichotomous outcomes will use default MIDs [RR thresholds of 0.80 and 1.2] • Other continuous outcomes will use default MIDs [0.5 times the SD of the control group]
Eligibility criteria – **study design**	• Systematic reviews of RCTs • RCTs • Comparative cohort studies (only if RCTs unavailable or limited data to inform decision making) Will consider conference abstracts only if related to RCTs
Other inclusion **exclusion criteria**	Community, residential, primary and secondary care. UK and non-UK studies. (Non UK studies from high income countries according to WHO/ World Bank criteria)

Proposed sensitivity/**sub-group analysis**, or meta-regression	No groups will be reviewed and analysed separately from the outset.
	
	In the presence of heterogeneity, the following subgroups will be considered for sensitivity analysis:
	• Population subgroups (e.g. age groups, presentation, severity:
	  ○ Ambulant vs. non-ambulant
	• Intervention subgroups (e.g. route of administration, drugs within drug classes, high/low dose):
	  ○ Drug dosage
	
	Important confounders (when comparative observational studies are included for interventional reviews)
	• Degree/severity of dystonia

Selection process – duplicate screening/selection/analysis	A random sample of the references identified in the search will be sifted by a second reviewer. This sample size will be 10% of the total, or 100 studies if the search identifies fewer than 1000 studies. All disagreements in study inclusion will be discussed and resolved between the two reviewers. The senior systematic reviewer or guideline lead will be involved if discrepancies cannot be resolved between the two reviewers

Field (based on PRISMA-P)	Content
Data management (software)	STAR was used to sift through the references identified by the search, and for data extraction Pairwise meta-analyses and production of forest plots was done using Cochrane Review Manager (RevMan5). 'GRADEpro' was used to assess the quality of evidence for each outcome.
Information sources – databases and dates	Database(s): Embase 1974 to Present, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; Cochrane Library; WEB OF SCIENCE
Identify if an update	Not an update
Author contacts	For details please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014.
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual 2014.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods see supplementary document C.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014.
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Alliance (NGA) and chaired by Dr Paul Eunson in line with section 3 of Developing NICE guidelines: the manual 2014.

Field (based on PRISMA-P)	Content
	Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not applicable

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CSF, cerebrospinal fluid; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; GMFCS, gross motor function classification system; HTA: Health Technology Assessment; ICF: International Classification of Functioning, Disability and Health; MID: minimally important difference; NICE: National Institute for Health and Care Excellence; NGA: National Guideline Alliance; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B – Literature search strategies

Literature search strategies for review question A3: Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?

This appendix is a combined search strategy and will be the same for all the evidence reviews for the A review questions as listed below:

A1: Which pharmacological treatments for spasticity (for example, enteral baclofen, tizanidine, diazepam, cannabinoids, and botulinum toxin injections) are most effective for improving motor function, participation and quality of life in adults with cerebral palsy?

A2: Are neurosurgical procedures (intrathecal baclofen pump and selective dorsal rhizotomy) effective in adults aged 19 and over with cerebral palsy to reduce spasticity and or dystonia?

A3: Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB)) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?

Database: Medline & Embase (Multifile)

Database(s): Embase 1974 to 2018 March 22, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Table 17: Last searched on 22 March 2018

#	Searches
1	exp Cerebral Palsy/ use prmz
2	exp cerebral palsy/ use oemezd
3	((cerebral or brain or central) adj2 (pal* or paralys#s or pares#s)).tw.
4	cerebral palsy.ti,ab.
5	little? disease.tw.
6	((hemipleg* or dipleg* or tripleg* or quadripleg* or unilateral*) adj5 spastic*).tw.
7	((hemipleg* or dipleg* or tripleg* or quadripleg* or unilateral*) adj3 ataxi*).tw.
8	or/1-6
9	limit 8 to english language
10	limit 9 to (adult <18 to 64 years> or aged <65+ years>) use oemezd [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process; records were retained]
11	limit 9 to "all adult (19 plus years)" [Limit not valid in Embase; records were retained]
12	11 use prmz
13	or/10,12
14	exp Muscle Spasticity/ use prmz
15	exp spasticity/ use oemezd
16	spastic*.tw.
17	exp Dystonia/
18	dystoni*.ti,ab.
19	abnormal muscle tone.ti,ab.
20	14 or 15 or 16 or 17 or 18 or 19
21	exp Muscle Spasticity/ or exp Dystonia/ or exp Infusion Pumps, Implantable/ or exp Physical

#	Searches
	Therapy Modalities/ or exp Rhizotomy/ or exp Splints/ or exp Orthotic Devices/ or exp Deep Brain Stimulation/ or exp Baclofen/ad, ae, tu or exp Botulinum Toxins/ad, ae, tu or exp Diazepam/ad, ae, tu or exp Cannabinoids/ad, ae, tu or exp Acetylcholine Release Inhibitors/ad, ae, tu or exp Muscle Relaxants, Central/ad, ae, tu or exp Levodopa/ad, ae, tu or exp Dantrolene/ad, ae, tu or exp Clonazepam/ad, ae, tu or exp Pregabalin/ad, ae, tu or exp Clonidine/ad, ae, tu or exp Trihexyphenidyl/ad, ae, tu or exp Tetrabenazine/ad, ae, tu or exp Anti-Dyskinesia Agents/ad, ae, tu
22	21 use prmz
23	exp implantable infusion pump/ or exp physiotherapy/ or exp dorsal rhizotomy/ or exp splint/ or exp orthosis/ or exp brain depth stimulation/ or exp baclofen/ae, ad, cb, dt or exp botulinum toxin/ae, ad, cb, dt or exp diazepam/ae, ad, cb, dt or exp cannabinoid/ae, ad, cb, dt or exp acetylcholine release inhibitor/ae, ad, cb, dt or exp central muscle relaxant/ae, ad, cb, dt or exp levodopa/ae, ad, cb, dt or exp tizanidine/ae, ad, cb, dt or exp gabapentin/ae, ad, cb, dt or exp dantrolene/ae, ad, cb, dt or exp clonazepam/ae, ad, cb, dt or exp pregabalin/ae, ad, cb, dt or exp clonidine/ae, ad, cb, dt or exp trihexyphenidyl/ae, ad, cb, dt or exp tetrabenazine/ae, ad, cb, dt
24	23 use oemezd
25	(physiotherap* or botulinum or baclofen or tizanidine or intrathecal baclofen pump or gabapentin or levodopa or dantrolene or clonazepam or pregabalin or clonidine or dorsal rhizotomy or tetrabenazine or trihexyphenidyl or lycra or DBS or deep brain stimulat* or splint* or serial cast*).ti,ab.
26	22 or 24 or 25
27	13 and 20
28	13 and 26
29	27 or 28
30	conference abstract.pt. use oemezd
31	letter.pt. or LETTER/ use oemezd
32	Letter/ use prmz
33	EDITORIAL/ use prmz
34	editorial.pt. use oemezd
35	NEWS/ use prmz
36	exp HISTORICAL ARTICLE/ use prmz
37	note.pt. use oemezd
38	ANECDOTES AS TOPIC/ use prmz
39	COMMENT/ use prmz
40	CASE REPORT/ use prmz
41	CASE REPORT/ use oemezd
42	CASE STUDY/ use oemezd
43	(letter or comment* or abstracts).ti.
44	or/30-43
45	RANDOMIZED CONTROLLED TRIAL/ use prmz
46	RANDOMIZED CONTROLLED TRIAL/ use oemezd
47	random*.ti,ab.
48	or/45-47
49	44 not 48
50	ANIMALS/ not HUMANS/ use prmz
51	ANIMAL/ not HUMAN/ use oemezd
52	exp ANIMALS, LABORATORY/ use prmz
53	exp ANIMAL EXPERIMENTATION/ use prmz

#	Searches
54	exp MODELS, ANIMAL/ use prmz
55	exp RODENTIA/ use prmz
56	NONHUMAN/ use oemezd
57	exp ANIMAL EXPERIMENT/ use oemezd
58	exp EXPERIMENTAL ANIMAL/ use oemezd
59	ANIMAL MODEL/ use oemezd
60	exp RODENT/ use oemezd
61	(rat or rats or mouse or mice).ti.
62	or/49-61
63	29 not 62
64	remove duplicates from 63

Database: Cochrane Library

Table 18: Last searched on 22 March 2018

#1	MeSH descriptor: [Cerebral Palsy] explode all trees
#2	((cerebral or brain or central) N2 (pal* or paralys?s or pare?s))
#3	((hemipleg* or dipleg* or tripleg* or quadripleg* or unilateral*) N5 spastic*)
#4	((hemipleg* or dipleg* or tripleg* or quadripleg* or unilateral*) N3 ataxi*)
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Muscle Spasticity] explode all trees
#7	MeSH descriptor: [Dystonia] explode all trees
#8	Dystoni* or spastic*
#9	#6 or #7 or #8
#10	MeSH descriptor: [Baclofen] explode all trees
#11	MeSH descriptor: [Botulinum Toxins] explode all trees
#12	MeSH descriptor: [Diazepam] explode all trees
#13	MeSH descriptor: [Cannabinoids] explode all trees
#14	MeSH descriptor: [Acetylcholine Release Inhibitors] explode all trees
#15	MeSH descriptor: [Muscle Relaxants, Central] explode all trees
#16	MeSH descriptor: [Infusion Pumps, Implantable] explode all trees
#17	MeSH descriptor: [Levodopa] explode all trees
#18	MeSH descriptor: [Physical Therapy Modalities] explode all trees
#19	physiotherap* or Botulinum or baclofen or tizanidine or intrathecal pump or gabapentin or levodopa
#20	MeSH descriptor: [Dantrolene] explode all trees
#21	MeSH descriptor: [Clonazepam] explode all trees
#22	MeSH descriptor: [Pregabalin] explode all trees
#23	MeSH descriptor: [Clonidine] explode all trees
#24	MeSH descriptor: [Trihexyphenidyl] explode all trees
#25	MeSH descriptor: [Rhizotomy] explode all trees
#26	MeSH descriptor: [Splints] explode all trees
#27	MeSH descriptor: [Orthotic Devices] explode all trees
#28	MeSH descriptor: [Deep Brain Stimulation] explode all trees
#29	MeSH descriptor: [Tetrabenazine] explode all trees

#1	MeSH descriptor: [Cerebral Palsy] explode all trees
#30	Tetrabenazine or Deep Brain Stimulation or DBS or Splint* or orthotic* or dorsal Rhizotomy or Trihexyphenidyl or Clonidine or Pregabalin or Clonazepam or Dantrolene or serial cast* or lycra or splint cast*
#31	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#32	#5 and #31
#33	#5 and #9
#34	#32 or #33

Database: Web of Science

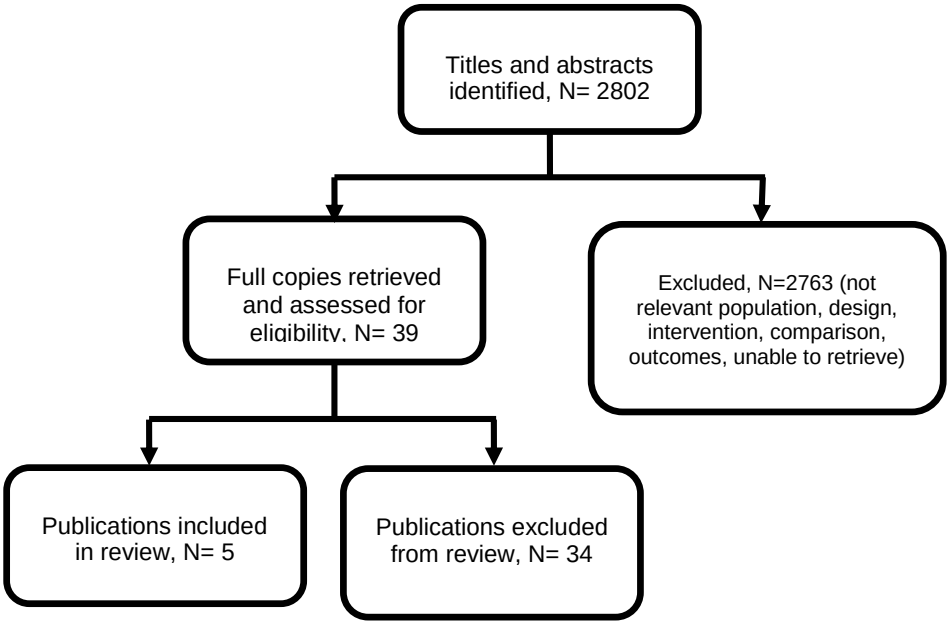
Table 19: Last searched on 27 March 2018

#6	#5 OR #3
#5	#4 AND #1
#4	ts=spasticity or ts=spastic* or ts=dystonia or ts=dystoni*
#3	#2 AND #1
#2	ts=physiotherap* or ts=Botulinum or ts=baclofen or ts=tizanidine or ts=intrathecal pump or ts=gabapentin or ts=levodopa or ts=Muscle Relaxant* or ts=Acetylcholine Release Inhibitor* or ts=Cannabinoid* or ts=Diazepam or ts=Tetrabenazine or ts=Deep Brain Stimulation or ts=DBS or ts=Splint* or ts=orthotic* or ts=dorsal Rhizotomy or ts=Trihexyphenidyl or ts=Clonidine or ts=Pregabalin or ts=Clonazepam or ts=Dantrolene or ts=serial cast* or ts=lycra or ts=splint cast*
#1	ts=Cerebral Palsy

Appendix C – Clinical evidence study selection

Clinical evidence study selection strategies for review question A3: Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?

Figure 10: Flow diagram of clinical article selection for interventions for dystonia review



Appendix D – Clinical evidence tables

Clinical evidence tables for review question A3: Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?

Table 20: Studies included in the evidence review for interventions for dystonia

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Koy, A., Pauls, K. A., Flossdorf, P., Becker, J., Schonau, E., Maarouf, M., Liebig, T., Fricke, O., Fink, G. R., Timmermann, L., Young adults with dyskinetic cerebral palsy improve subjectively on pallidal stimulation, but not in formal dystonia, gait, speech and swallowing testing, European Neurology, 72, 340-8, 2014 **Ref Id** 342613 **Country/ies where the study was carried out** Germany **Study type** Before-and-after study **Aim of the study**	**Sample size** N=8 **Characteristics** Diagnosis: dyskinetic cerebral palsy Age: mean age at DBS operation was 26.1 ± 6.5 years (range 16.1–33.8 years). Degree/severity of dystonia: mean preoperative BFMDRS-M was 64.5 ± 38.4 Ambulant: GMFCS III - 3/8, GMFCS II - 2/8, Non-ambulant: GMFCS V - 3/8 **Inclusion criteria** Ptients with dyskinetic cerebral palsy who underwent GPi-DBS surgery at the University Hospital of Cologne between	**Interventions** Bilateral pallidal deep brain stimulation	**Details** Using pre and postoperative videos the severity of dystonia was assessed using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). BFMDRS, subjective impression of the extent of post-operative change as well as gait (Leonardo Mechanograph), speech (Frenchay Dysarthria) and swallowing performances (fiberoptic laryngoscopy) were assessed postoperative while the stimulator was ‘on’ and ‘off’. The ‘off’ status was defined pragmatically as a minimum of 12 hours prior to assessment. Duration of follow-up ranged from 9 to 83 months	**Outcomes** Dystonia (follow up mean 3.7 years; range 9 months to 6.9 years) **Results** see Forest plots in appendix E	**Limitations** EPOC Quality criteria for interrupted time series (ITS) Protection against secular changes - not clear Data were analysed appropriately - done Sample size calculation performed - not done Shape of the intervention effect was specified - done Protection

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To measure the effect of bilateral pallidal deep brain stimulation on dystonia, gait, speech, swallowing and subjective change of symptoms. **Study dates** 2003-2011 **Source of funding** Clinical Research Group 219 by the German Research Foundation (DFG).	2003 and 2011. No other criteria reported. **Exclusion criteria** Not reported.				against detection bias: Intervention unlikely to affect data collection - done Protection against detection bias: Blinded assessment of primary outcome(s) - done **Other information**
Full citation Marks, W. A., Honeycutt, J., Acosta, F., Reed, M., Bailey, L., Pomykal, A., Mercer, M., Dystonia due to cerebral palsy responds to deep brain stimulation of the globus pallidus internus, Movement Disorders, 26, 1748-1751, 2011 **Ref Id** 381853 **Country/ies where the study was carried out**	**Sample size** N=6 (aged over 16) **Characteristics** Diagnosis: Age: mean age 20.65 ± 3.55 years (range, 17–26 years) Degree/severity of dystonia: preoperative BFMDRS-M 91.50 ± 9.75 Ambulant: not reported	**Interventions** Bilateral pallidal deep brain stimulation.	**Details** Preoperative motor function was assessed using the Burke-Fahn-Marsden Dystonia Movement and Disability scales and the Barry Albright Dystonia Scale. This was measured again after DBS. Follow-up 6 months	**Outcomes** Dystonia (follow up 6 months) **Results** see Forest plots in appendix E	**Limitations** EPOC Quality criteria for interrupted time series (ITS) Protection against secular changes - done Data were analysed appropriately - done Sample size

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
USA **Study type** Before-and-after study **Aim of the study** To describe the effect of DBS in children / yound adults with CP. **Study dates** 2008 - 2010 **Source of funding** Not reported. Relevant conflicts of interest/financial disclosures: Nothing to report.	Non-ambulant: not reported **Inclusion criteria** People with cerebral palsy and dystonia that was incompletely responsive to oral agents, failed response or inability to tolerate intrathecal baclofen, cognitive ability to benefit from relief of dystonia, and adequate family support. **Exclusion criteria** Not reported				calculation performed - not done Shape of the intervention effect was specified - done Protection against detection bias: Intervention unlikely to affect data collection - done Protection against detection bias: Blinded assessment of primary outcome(s) - not clear **Other information**
Full citation Pozin, I., Bdolah-Abram, T., Ben-Pazi, H., Levodopa does not improve function in individuals with dystonic cerebral palsy, Journal of Child	**Sample size** N=9 **Characteristics** Diagnosis: all had quadriplegic	**Interventions** Levodopa: maximal daily dose (according to weight) was 150 mg/d (<15	**Details** Participants were randomized into 2 groups. Group 1 was treated for 2 weeks first with levodopa (Dopicar 1) and,	**Outcomes** Motor function using functional measures	**Limitations** Cochrane risk of bias Random sequence

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Neurology, 29, 534-7, 2014 **Ref Id** 342861 **Country/ies where the study was carried out** Israel **Study type** Randomised cross-over trial **Aim of the study** To measure the effect of levodopa on upper limb function in people with cerebral palsy. **Study dates** 2010 - 2012 **Source of funding** Partially supported by ILAN, The Israeli Foundation for Handicapped Children.	cerebral palsy Age: mean 16.8 + 5.6 years (range 8 to 27 years) Degree/severity of dystonia: bilateral dystonia disabling upper limb function. Ambulant: not reported - GMFCS ranged from 3 to 5 Non-ambulant: not reported **Inclusion criteria** People with cerebral palsy aged 6-30 years, bilateral dystonia disabling upper limb function and sufficient cognitive function to complete the tasks. **Exclusion criteria** Diurnal fluctuations, parkinsonian features, appearance of symptoms during childhood, or other clinical signs and symptoms suggesting an inborn error of metabolism or genetic cause, use of medications for dystonia or surgical treatment during the time of the study.	kg), 200 mg/d (16-40 kg), 300 mg/d (41-55 kg), 400 mg/d (>55 kg). Mean dose 6.65 + 1.66 mg/kg. Placebo	following a 2-week washout period, another 2 weeks on placebo. Group 2 was treated first with placebo, 2-week washout period and then with levodopa. Participants were assessed before starting each medication and on maximal dose, 1-3 hours after receiving the last dose. Primary outcome measure was upper limb function assessed using the Quality of Upper Extremity Skills Test. Secondary outcome measures were dynamometer recordings of maximal pinch and grip strength, box-and-blocks test, and the 9-hole pegs test. Both examiners and participants were blinded to assigned treatment.	Adverse events (follow-up 2 weeks) **Results** see Forest plots in appendix E	generation - unclear risk Allocation concealment - low risk Blinding of participants and personnel - low risk Blinding of outcome assessment - low risk Incomplete outcome data. - low risk Selective reporting -low risk Other sources of bias - not applicable Overall - low risk of bias **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Outcomes**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Romito, L. M., Zorzi, G., Marras, C. E., Franzini, A., Nardocci, N., Albanese, A., Pallidal stimulation for acquired dystonia due to cerebral palsy: beyond 5 years, European Journal of Neurology, 22, 426-e32, 2015 **Ref Id** 382180 **Country/ies where the study was carried out** Italy **Study type** Before and after study **Aim of the study** To measure the efficacy and safety of GPi DBS for the treatment of generalized dystonia due to CP **Study dates** Not reported **Source of funding** Not reported	N=15 **Characteristics** Diagnosis: Dystonia & CP Age: mean age at implant 29.8 years (SD 9.5 years; range 15 to 42 years) Degree/severity of dystonia: preoperative BFMDRS motor score - mean 72 (SD 22.7) Ambulant: not reported Non-ambulant: not reported **Inclusion criteria** Persistent dystonia (with generalized distribution and static course), Ashworth score <2 in any segment, mild static brain MRI abnormalities **Exclusion criteria** Cognitive (Mini-Mental State Examination score >24) or psychiatric abnormalities.	Bilateral pallidal deep brain stimulation (mean follow up 4.4 years; SD 1.8 years)	Dystonia severity was assessed preoperatively, at 1–3 months after implant and then at yearly intervals using the motor section of the Burke Fahn Marsden dystonia rating scale (BFMDRS). HRQoL was measured using SF-36	Health related quality of life Dystonia Adverse events (mean follow up 4.4 years) **Results** see Forest plots in appendix E	EPOC Quality criteria for interrupted time series (ITS) Protection against secular changes - done Data were analysed appropriately - done Sample size calculation performed - not done Shape of the intervention effect was specified - done Protection against detection bias: Intervention unlikely to affect data collection - done Protection against detection bias: Blinded assessment of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					primary outcome(s) - not clear **Other information**
Full citation Vidailhet, M., Yelnik, J., Lagrange, C., Fraix, V., Grabli, D., Thobois, S., Burbaud, P., Welter, M. L., Xie-Brustolin, J., Braga, M. C. C., Ardouin, C., Czernecki, V., Klinger, H., Chabardes, S., Seigneuret, E., Mertens, P., Cuny, E., Navarro, S., Cornu, P., Benabid, A. L., LeBas, J. F., Dormont, D., Hermier, M., Dujardin, K., Blond, S., Krystkowiak, P., Destee, A., Bardinet, E., Agid, Y., Krack, P., Broussolle, E., Pollak, P., Bilateral pallidal deep brain stimulation for the treatment of patients with dystonia-choreoathetosis cerebral palsy: a prospective pilot study, The Lancet Neurology, 8, 709-717, 2009 **Ref Id** 587640 **Country/ies where the study was carried out** France	**Sample size** N=13 **Characteristics** Diagnosis: dystonia-choreoathetosis CP Age: median age 33 years [range 20–44] Degree/severity of dystonia: preop BFMDRS movement scale - mean 44.23 (SD 21.2) Ambulant: not reported Non-ambulant: not reported **Inclusion criteria** Disabling dystonia, defined as involuntary sustained muscle contractions that led to abnormal movements and postures, which could be multifocal or generalised, with a combination of segmental crural dystonia (one leg and the trunk)	**Interventions** Bilateral pallidal deep brain stimulation.	**Details** Patients were assessed before surgery and after 1 year of continuous therapeutic neurostimulation. The patients were scored by an expert in movement disorders, in random order, on standardised, anonymised videos. Cognitive functions and mood were also assessed before surgery and after 1 year of therapeutic neurostimulation with the MMSE, the progressive matrices of the Raven PM-38, the similarities and arithmetic subtests of the revised Wechsler adult intelligence scale (WAIS-R), the free and cued selective reminding test (Grober and Buschke test), and the Wisconsin card sorting test. Mood was assessed with the Beck depression inventory for mood. Health-related quality of life was assessed with a validated French version of the	**Outcomes** Health related quality of life Dystonia Adverse events Pain (follow up 1 year) **Results** see Forest plots	**Limitations** EPOC Quality criteria for interrupted time series (ITS) Protection against secular changes -done Data were analysed appropriately - done Sample size calculation performed - not clear Shape of the intervention effect was specified - done Protection against detection bias:

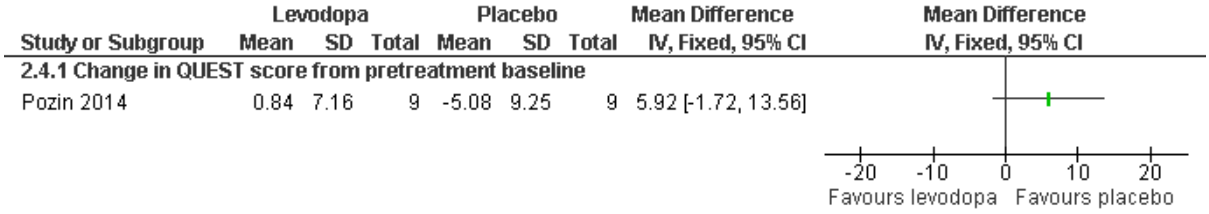
Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Before and after study **Aim of the study** To measure the effectiveness of bilateral pallidal-DBS in adults with dystonia-choreoathetosis CP **Study dates** 2003 tp 2006 **Source of funding** National PHRC; Cerebral Palsy Foundation: Fondation Motrice/APETREIMC; French INSERM Dystonia National Network; Medtronic. One author was a paid consultant for Medtronic. The other authors declared no conflicts of interest.	and involvement of any other segment (face, neck, or upper or lower limbs); neonatal hypoxic or ischaemic encephalopathy 2 and delayed early motor milestones (eg, sitting or walking); no other cause of dystonia, including metabolic and genetic disorders, focal vascular lesions, head trauma or neuroleptic treatments; little or no spasticity (Ashworth score <2 for each segment); no more than slight abnormalities seen on T1-weighted MRI (decreased grey–white matter contrast with partial disappearance of the basal ganglia and minimum atrophy of the pallidum or putamen); and optimum pharmacological treatments (ie, the highest tolerated doses of drugs known to be useful in dystonia, including levodopa and anticholinergics) were ineffective **Exclusion criteria** Psychiatric disorders, cognitive impairment (mini-mental state examination [MMSE] score <=24);		medical outcomes study 36-item short-form (SF-36) general health survey questionnaire. Pain was assessed with a visual analogue scale (max–min [0–10]). The Hopkins symptom checklist (SCL-90), a self-rating symptom scale, was used to measure changes in psychological status over time.		Intervention unlikely to affect data collection - done Protection against detection bias: Blinded assessment of primary outcome(s) - done **Other information**

Appendix E – Forest plots

Forest plots for review question A3: Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?

Comparison 1. Levodopa versus placebo

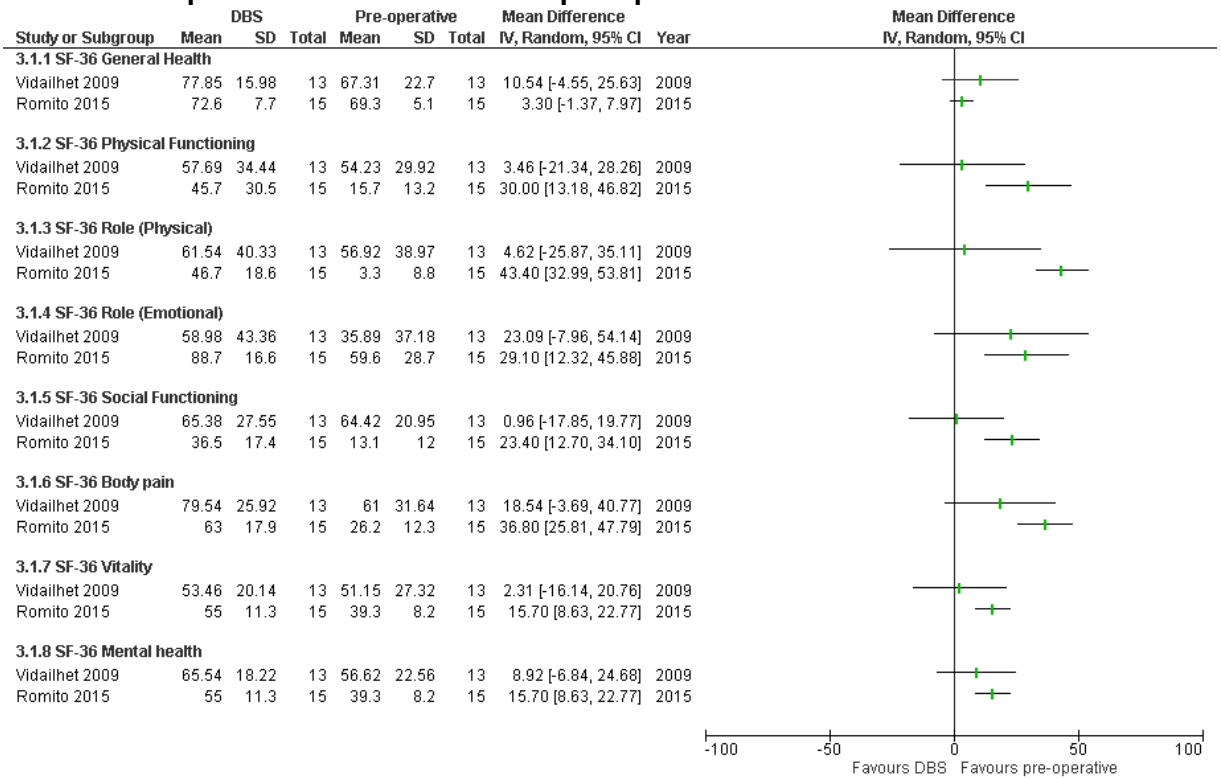
Figure 11: Change in motor function from pre-treatment with levodopa versus placebo, at 2 weeks of follow-up



CI: confidence interval; IV: inverse variance; QUEST: Quality of Upper Extremity Skills Test; SD: standard deviation

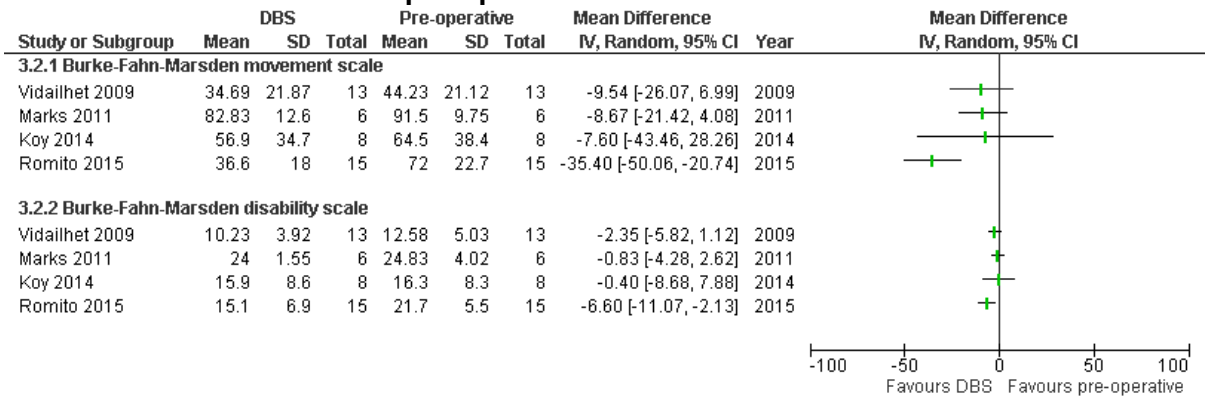
Comparison 2. Bilateral pallidal deep brain stimulation: post versus pre-operative

Figure 12: Health related quality of life after one to four years of bilateral pallidal deep brain stimulation versus pre-operative



CI: confidence interval; IV: inverse variance; DBS: deep brain stimulation; SD: standard deviation; SF-36: 36-Item Short Form Health Survey

Figure 13: Dystonia after 6 months to 4 years of bilateral pallidal deep brain stimulation versus pre-operative



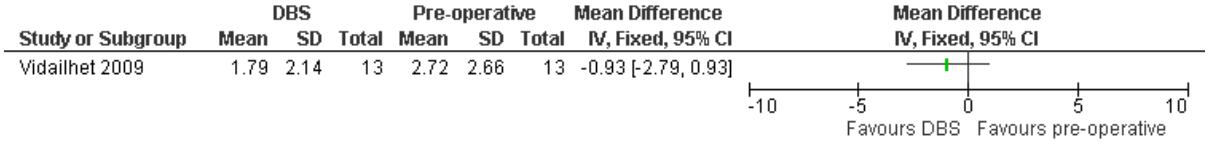
CI: confidence interval; IV: inverse variance; DBS: deep brain stimulation; SD: standard deviation

Figure 14: Adverse events during 1 to 4 years of bilateral pallidal deep brain stimulation

	DBS	
Study or Subgroup	**Events**	**Total**
3.5.1 Hypophonia		
Romito 2015	2	15
3.5.2 Dysarthria		
Romito 2015	4	15
3.5.3 Local pain		
Romito 2015	2	15
Vidailhet 2009	1	13
3.5.4 Paraesthesia		
Romito 2015	2	15
3.5.5 Anxiety		
Vidailhet 2009	5	13
3.5.6 Stimulation adjusted due to insufficient benefit		
Vidailhet 2009	4	13
3.5.7 Stimulator failure (exposure to magnetic field)		
Vidailhet 2009	1	13

DBS: deep brain stimulation

Figure 15: Pain after one year of bilateral pallidal deep brain stimulation compared to baseline



CI: confidence interval; IV: inverse variance; DBS: deep brain stimulation; SD: standard deviation

Appendix F – GRADE tables

GRADE tables for review question A3: Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?

Table 21: Clinical evidence profile: levodopa versus placebo

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levodopa	placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
HRQoL - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Dystonia - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Satisfaction - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Change in motor function from pre-treatment (follow up: 2 weeks; assessed with: QUEST score; Scale from: 0 to 100)												
1	randomised trials	serious [1]	not serious	not serious	serious [2]	none	9	9	-	MD 5.92 % higher (1.72 lower to 13.56 higher)	LOW	CRITICAL
Adverse events												
1	randomised trials	very serious [1,3]	not serious	not serious	serious [2]	none	No adverse events reported [4]				VERY LOW	IMPORTANT
Goal attainment scores - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levodopa	placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Pain - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: confidence interval; HRQoL: health related quality of life; MD: mean difference
1 Unclear randomisation method
2. Confidence interval for effect includes one default MID threshold
3. Adverse events were not systematically monitored.
4. No events reported

Table 22: Clinical evidence profile: bilateral pallidal deep brain stimulation versus pre-operative

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral pallidal deep brain stimulation	preoperative	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
HRQoL (follow up: range 1 years to 4 years; assessed with: SF-36 General Health; Scale from: 0 to 100; Higher better)												
2	observational studies	not serious	not serious	not serious	serious[2]	none	28	28	-	HRQoL after DBS ranged from 3.30 higher to 10.54 higher	VERY LOW	CRITICAL
HRQoL (follow up: range 1 years to 4 years; assessed with: SF-36 Physical Functioning; Scale from: 0 to 100; Higher better)												
2	observational studies	not serious	serious b	not serious	serious[2]	none	28	28	-	HRQoL after DBS ranged from 3.46 higher to 30.00 higher	VERY LOW	CRITICAL
HRQoL (follow up: range 1 years to 4 years; assessed with: SF-36 Role (Physical); Scale from: 0 to 100; Higher better)												

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral pallidal deep brain stimulation	preoperative	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
2	observational studies	not serious	not serious	not serious	serious[2]	none	28	28	-	HRQoL after DBS ranged from 4.62 higher to 43.40 higher	VERY LOW	CRITICAL
HRQoL (follow up: range 1 years to 4 years; assessed with: SF-36 Role (Emotional); Scale from: 0 to 100; Higher better)												
2	observational studies	not serious	not serious	not serious	serious[2]	none	28	28	-	HRQoL after DBS ranged from 23.09 higher to 29.10 higher)	VERY LOW	CRITICAL
HRQoL (follow up: range 1 years to 4 years; assessed with: SF-36 Social Functioning; Scale from: 0 to 100; Higher better)												
2	observational studies	not serious	not serious	not serious	serious[2]	none	28	28	-	HRQoL after DBS ranged from 0.96 higher to 23.40 higher	VERY LOW	CRITICAL
HRQoL (follow up: range 1 years to 4 years; assessed with: SF-36 Body pain; Scale from: 0 to 100; Higher better)												
2	observational studies	not serious	not serious	not serious	serious[2]	none	28	28	-	HRQoL after DBS ranged from 18.54 higher to 36.80 higher	VERY LOW	CRITICAL
HRQoL (follow up: range 1 years to 4 years; assessed with: SF-36 Vitality; Scale from: 0 to 100; Higher better)												
2	observation	not	not serious	not	serious[3]	none	28	28	-	HRQoL after DBS	VERY	CRITICAL

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral pallidal deep brain stimulation	preoperative	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
	al studies	serious		serious						ranged from 2.31 higher to 15.70 higher	LOW	
HRQoL (follow up: range 1 years to 4 years; assessed with: SF-36 Mental health; Scale from: 0 to 100; Higher better)												
2	observational studies	not serious	not serious	not serious	serious[2]	none	28	28	-	HRQoL after DBS ranged from 8.92 higher to 15.70 higher	VERY LOW	CRITICAL
Dystonia (follow up: range 6 months to 4 years; assessed with: Burke-Fahn-Marsden movement scale; Scale from: 0 to 120; Lower better)												
4	observational studies	not serious	not serious	not serious	serious[2]	none	42	42	-	Dystonia after DBS ranged from 7.60 lower to 35.40 lower	VERY LOW	CRITICAL
Dystonia (follow up: range 6 months to 4 years; assessed with: Burke-Fahn-Marsden disability scale ; Scale from: 0 to 30; Lower better)												
4	observational studies	not serious	not serious	not serious	serious[2]	none	42	42	-	Dystonia after DBS ranged from 0.40 lower to 6.60 lower	VERY LOW	CRITICAL
Satisfaction - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Motor function - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral pallidal deep brain stimulation	preoperative	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Adverse events - Hypophonia (follow up: 4 years)												
1	observational studies	serious[4]	not serious	not serious	serious[2]	none	Rate was 2/15 (13%)				VERY LOW	IMPORTANT
Adverse events - Dysarthria (follow up: 4 years)												
1	observational studies	serious[4]	not serious	not serious	serious[2]	none	Rate was 4/15 (27%)				VERY LOW	IMPORTANT
Adverse events - Local pain (follow up: range 1 years to 4 years)												
2	observational studies	serious[4]	not serious	not serious	serious[2]	none	Rate ranged from 1/13 (8%) to 2/15 (13%)				VERY LOW	IMPORTANT
Adverse events - Paraesthesia (follow up: 4 years)												
1	observational studies	serious[4]	not serious	not serious	serious[2]	none	Rate was 2/15 (13%)				VERY LOW	IMPORTANT
Adverse events - Anxiety (follow up: 1 years)												
1	observational studies	serious[4]	not serious	not serious	serious[2]	none	Rate was 5/13 (38%)				VERY LOW	IMPORTANT
Adverse events - Stimulation adjusted due to insufficient benefit (follow up: 1 years)												
1	observational studies	serious[4]	not serious	not serious	serious[2]	none	Rate was 4/13 (31%)				VERY LOW	IMPORTANT
Adverse events - Stimulator failure (exposure to magnetic field) (follow up: 1 years)												
1	observational studies	serious[4]	not serious	not serious	serious[2]	none	Rate was 1/13 (8%)				VERY LOW	IMPORTANT
Goal attainment scores - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Pain (follow up: 1 years)												
1	observational studies	not seriou	not serious	not serious	serious[2]	none	13	13	-	MD 0.93	VERY LOW	IMPORTANT

Quality assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bilateral pallidal deep brain stimulation	preoperative	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
		s								lower (2.79 lower to 0.93 higher)		

Appendix G – Economic evidence study selection

Economic evidence study selection for review question A3: Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?

No economic evidence was identified for this review

Appendix H – Economic evidence tables

Economic evidence tables for review question A3: Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?

No economic evidence was identified for this review.

Appendix I – Health economic evidence profiles

Health economic evidence profiles for review question A3: Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?

No economic evidence was identified for this review.

Appendix J – Health economic analysis

Health economic analysis for review question A3: Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?

Model structure

A decision analytic model was developed in Microsoft Excel® (2013) from the perspective of the UK NHS and using 2015/16 costs. The model takes the form of a state transition model. The first cycle lasts 2 weeks to reflect the duration of the procedure and complications associated with the procedure, whilst the second cycle lasts 1 month to reflect the risk of postoperative events. Subsequent cycles are 12 months long.

The model takes a lifetime horizon since cerebral palsy is a chronic conditions associated with on-going medical management, rather than a cure. DBS is a permanent procedure, hence it is important to capture those benefits that may persist for the remainder of the individual's life. Adults with dystonia enter the model aged 19 as the committee considered patients to be eligible for DBS from this age.

Cost-effectiveness results should reflect the present value of the stream of costs and benefits accruing over the time horizon of the analysis. NICE considers that it is usually appropriate to discount costs and health effects at the same annual rate of 3.5%, based on the recommendations of the UK Treasury for the discounting of costs (NICE 2017 Methods Manual). Consequently the model has adopted a discount rate of 3.5% for both costs and benefits (QALYs, quality adjusted life years), but this input can be varied by the user in the model.

During the first cycle (the procedure) patients may experience a seizure, infection, intracranial haemorrhage (ICH), or die. Patients who experience an infection could either remain on DBS, or abandon DBS and receive "usual care". Patients who experience a seizure remain on DBS treatment based on the assumption that seizures stabilise following immediate treatment. Patients who experience a symptomatic ICH with recovery or asymptomatic ICH (referred to as "minor ICH" in this document) continue with DBS, or transition to "usual care". Patients who experience a symptomatic ICH with deficit (referred to as "major ICH" in this document) abandon DBS and receive long-term ICH care. Following a successful procedure for DBS, patients remain on DBS and receive a routine implanted pulse generator (IPG) replacement every 5 years (frequency varied in sensitivity analysis). Each year patients on DBS are at risk of a hardware failure which will incur additional surgery to correct. Patients in usual care receive pharmacological treatment in the base case, but alternative treatments are explored in sensitivity analysis.

It is important to note that the severity of an ICH will depend on symptoms and the subsequent effect on function and quality of life. Whereas, the volume of blood, location of the blood, and timing of the bleed intraoperatively would determine if the DBS hardware is abandoned or not. However, it was not possible to capture all of these eventualities in the model, as evidence was not available to inform those possibilities. As a result, committee opinion was used alongside the best available evidence to justify the assumptions this model has made with regards to this complication and others.

Patients in usual care are at a low risk of many minor adverse events such as drowsiness, confusion, urinary problems and at a lower risk of serious adverse events such as allergic reactions, seizures and arrhythmias. The committee also added that adults with cerebral palsy who receive other (non-dystonia related) treatments would also be at risk of those

adverse events. Given the small number of people that would enter those health states, the total treatment cost and QALY loss attached to them would be negligible. Moreover, the clinical evidence review identified no studies that reported the adverse effects of pharmacological treatment for dystonia in adults with cerebral palsy. As a result, it was assumed patients in usual care are not at risk of any adverse events as the added complexity to the model would have a negligible impact on the results. For completeness, implications of omitting the adverse effects of usual care are discussed.

The structure of the model is illustrated in Figure 16 and described in more detail in Table 23.

Figure 16: Model structure

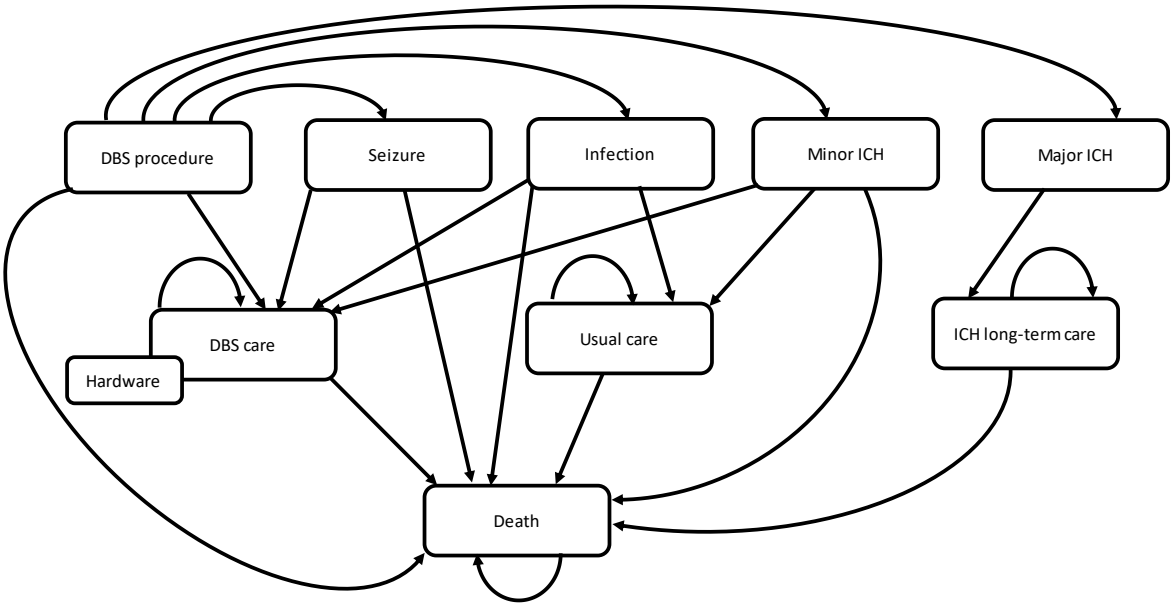


Table 23: Description of health states

Health state	Description
DBS procedure (without complications)	Patients enter the model in this health state in cycle 0. Patient incur the cost of the procedure and are at risk of a seizure, infection, ICH or death (procedure related and cerebral palsy related death) in the first cycle. Patients who do not experience a DBS-related complication or death, transition to DBS care.
DBS care	Patients enter this health state following a DBS procedure (with or without a seizure, infection or minor ICH). Patients can remain in this health state for more than one cycle. A proportion of patients in this health state experience a hardware failure, incurring a treatment cost and disutility. Patients receive replacement IPGs every 5 years to maintain their equipment. Patients are at risk of cerebral palsy related mortality.
Seizure	Patients are at risk of a seizure in the first 2 cycles. Patients remain in this health state for one cycle (tunnel state). A seizure is associated with a treatment cost and a disutility. Patients remain on DBS following a seizure. Patients are at risk of cerebral palsy related mortality plus an increased risk.
Infection	Patients are at risk of an infection in the first 2 cycles, the first cycle (during the procedure) is associated with a lower risk.

Health state	Description
	Patients remain in this health state for one cycle (tunnel state). An infection is associated with a treatment cost and disutility. A proportion of patients remain on DBS whilst the remaining proportion who do not die abandon DBS care and receive "usual care". Patients are at risk of cerebral palsy related mortality plus an increased risk.
Minor ICH (symptomatic with recovery or asymptomatic)	Patients are at risk of a minor ICH in the first cycle (during the procedure). Patients remain in this health state for one cycle (tunnel state). A minor ICH is associated with a treatment cost and a disutility. A proportion of patients remain on DBS whilst the remaining proportion who do not die abandon DBS care and receive "usual care". Patients are at risk of cerebral palsy related mortality plus an increased risk.
Major ICH (symptomatic with deficit)	Patients are at risk of a major ICH in the first cycle (during the procedure). Patients remain in this health state for one cycle (tunnel state). A major ICH is associated with a treatment cost and a disutility. All patients abandon DBS care and receive long-term ICH care. Patients are at risk of cerebral palsy and major ICH related mortality.
ICH long-term care	Patients enter this health state following a major ICH. Patients receive long-term ICH care and incur a disutility over their lifetime. Patients are at risk of cerebral palsy and long-term ICH related mortality.
Usual care	Patients enter this health state following an infection or minor ICH. Patients can remain in this health state for more than one cycle. Patients receive trihexyphenidyl (5mg daily) in the base to align with the type of pre-treatment participants received in Vidailhet 2009 and Romito 2015 and the type of pharmacological treatment used in clinical practice today. Botulinum toxin administered every 6 months is explored as a sensitivity analysis.
Death	Terminal state where the risk is based on cerebral palsy related mortality. The initial DBS procedure and major ICHs increase the risk of mortality. No utility or costs are incurred.

DBS: Deep Brain Stimulation; ICH: intracranial haemorrhage.

Clinical effectiveness

Probability of DBS-related complications

DBS-related complications were included in the model as they can have important cost and QALY implications. The trials included in the clinical evidence review were small and unrepresentative of the adverse effects seen in practice, so alternative papers that analysed DBS were sought to inform the probability of complications in the model.

Boviatsis 2010 and Voges 2006 reviewed the complications of DBS experienced by their departments; from 2003 to 2010 in 106 patients and from 1996 to 2003 in 262 patients, respectively. Both also compared their own results to others reported in the literature.

Both of those papers considered ICHs to be important and serious adverse events associated with DBS, reporting probabilities in their own departments of 1.9% (2 of 106 patients) and 0.4% (1 of 262 patients) and higher results in the literature they reviewed (Beric 20013.3%; Kondziolka 2002, 1.5%; Oh 2002, 3.6%; Umemura 2003, 3.6%; Limousin 1999, 2.7%; Lyons 2004, 1.2%). However, details on the event, such as the severity, were not reported. As a result, the committee sought the paper by Binder 2005 who examined symptomatic and asymptomatic haemorrhages across all 280 DBS procedures performed for movement disorders between June 1998 and May 2004.

Skin infection may be caused by both DBS surgery and implanted hardware components. Consequently, the definition of infection in the literature was not unanimous; some restricted the definition to hardware-involving infections with positive only cultures, whereas others also included superficial infections over the implanted hardware. As a result, the model considered early infections in the first cycle, later infections in the second cycle and antibiotic treatment to remain on DBS, or removal of the system.

Table 24 below presents the probability of perioperative DBS-related complications used in the model.

Table 24: Probability of perioperative DBS-related complications

Complication	Probability	Source and notes
Seizure	0.9%	Boviatsis 2010 stated that epileptic seizures can occur occasionally in patients undergoing DBS and reported a rate of 0.9% in their department. Voges also found a low risk in their review of the literature where 3 of the 7 studies reported cases of seizures (Beric 2001, 2.3%; Umemura 2003, 0.9%; Lyons 2004, 1.2%)
Infection first cycle	1.5%	Voges 2006 registered a total of 15 skin infections in 262 (5.7%) patients. The infection rate during the first observation period was 1.5% (4/262 patients) and the late infection rate after the initial surgery was 6.1% (11/180 patients). Voges 2006 concluded that their data are in line with infection rates given in the literature, ranging from 1.2% to 15.2%.
Infection second cycle	6.1%	
Remain on DBS following infection	20%	Three of those 15 patients in Voges 2006 were successfully treated with systemic antibiotics, but removal of the system was necessitated in the remaining 12.
Switch to usual care following infection	80%	
ICH minor	2.7%	Binder 2005: symptomatic with recovery (10/481) or asymptomatic (3/481)
ICH major	0.6%	Binder 2005: symptomatic with deficit (3/481)
Switch to usual care following minor ICH	23%	CT scanning instead of MRI was performed by Binder 2005 in 3 patients who had procedures aborted because of intraoperative neurological deficit (3/13)
Remain on DBS following Minor ICH	77%	It is not documented in Binder 2005 whether the other (10) intra-operative bleeds had their procedure aborted, or not. However, given that they could safely have a MRI, it is assumed DBS was completed (10/13).

DBS: Deep Brain Stimulation; MRI: Magnetic Resonance Imagining

According to the committee, hardware-related failures can occur at any time during or after the procedure. Bovistis 2010 defined hardware failures as an electrode breakage, lead or extension fracture or migration or misplacement and found those to be experienced by 4 of 106 patients (3.8%) in their department. Voges 2006 reviewed the literature and found lead fractures to range from 1.7% (Voges 2006) to 15.2% (Kondziolka 2002), lead migrations from 1.5% (Kondziolka 2002) to 6.3% (Lyons 2004) and extension wires from 1.1% (Voges 2006) to 3.5% (Beric 2001). However, they also found zero cases reported for each type of hardware failure. In their own study, Voges 2006 reported hardware-related problems in 25 of 180 (13.9%) of patients during their long-term observation. In the model an annual probability of 4.0% was used to reflect a weighted average of those papers. The methods and data used to obtain this value is provided in Table 25.

Table 25: Probability of hardware-related complications

Parameter	Beric 2001	Kondziolka 2002	Oh 2002	Lyons 2004	Voges 2006	Bovistis 2010
Duration (years)	3.5	2.4	2.8	5.0	2.9	7
Participants	86	66	79	80	180	106
Reported probability over study duration	0.094	0.182	0.140	0.151	0.139	0.038
Rate	0.028	0.083	0.055	0.033	0.051	0.006
1-year probability	0.028	0.080	0.053	0.032	0.050	0.006
Weighted 1-year probability by number of participants	**0.04**					

Rate = - (ln (1-probability)) / duration
1-year probability = 1 – exp (-rate x1)

Health-related quality of life

The QALY is NICE's preferred measure of benefit for economic evaluation. This is because it can be seen as a generic measure of health which allows a comparison across treatments which affect different dimensions of health.

The QALY reflects the 2 principle objectives of health care:

- increase longevity;
- increase quality of life.

Estimating a QALY involves placing a quality of life weight on a particular health state. This quality weight lies between 0 and 1, where 1 denotes full or 'perfect health' and 0 denotes death. Based on a need for consistency across appraisals and guidelines, NICE favours the EQ-5D to value health states - a generic, preference based measure which comes with pre-existing utility values obtained from a representative sample of the UK general population, although others measures and value sets are available.

Clinical effectiveness data (specifically health-related quality of life data) was taken from 2 before and after type studies (Vidailhet 2009 and Romito 2015) that reported the results for each of the 8 domains of the SF-36, pre- and post- DBS treatment. To allow for subsequent use in the health economic analyses, the SF-36 was mapped on to the EQ-5D using the mapping regression coefficients produced by Ara and Brazier 2008 (Table 26).

Table 26: EQ-5D regression coefficients

Domain	Mean
Intercept	0.0326
PF, physical functioning	0.0037
SF, social functioning	0.0011
RP, role physical	-0.0002
RE, role emotional	0.0002
MH, mental health	0.0026
VT, vitality	-0.0006
BP, bodily pain	0.0029
GH, general health	0.0005

Table 27: Vidailhet 2009

Domain	Pre-DBS	1 year post-DBS
Intercept	NA	NA
PF, physical functioning	54.23	57.69
SF, social functioning	64.42	65.38
RP, role physical	56.92	61.54
RE, role emotional	35.89	58.98
MH, mental health	52.62	65.54
VT, vitality	51.15	53.46
BP, bodily pain	61.00	79.54
GH, general health	67.31	77.85
EQ-5D value [a]	**0.61**	**0.72**

*3. eq5d[i] = intercept + (PF[i]*bPF) + (SF[i]*bSF) + (RP[i]*bRP) + (RE[i]*bRE) + (MH[i]*bMH) + (VT[i]*bVT) + (BP[i]*bBP) + (GH[i]*bGH)*

Table 28: Romito 2015

Domain	Pre-DBS	1 year post-DBS	2 years post-DBS	Last visit
Intercept	NA	NA	NA	NA
PF, physical functioning	15.7	45.7	48.7	50.0
SF, social functioning	13.1	36.5	37.3	38.2
RP, role physical	3.3	46.7	55.0	56.7
RE, role emotional	59.6	88.7	86.4	90.6
MH, mental health	54.9	69.6	72.0	73.9
VT, vitality	39.3	55.0	56.0	58.0
BP, bodily pain	26.2	63.0	70.5	69.1
GH, general health	69.3	72.6	73.0	73.0
EQ-5D value [a]	**0.35**	**0.61**	**0.65**	**0.66**

*(b) eq5d[i] = intercept + (PF[i]*bPF) + (SF[i]*bSF) + (RP[i]*bRP) + (RE[i]*bRE) + (MH[i]*bMH) + (VT[i]*bVT) + (BP[i]*bBP) + (GH[i]*bGH)*

Given that no comparative data was identified, it was assumed the utility pre-DBS is equivalent to the utility associated with "usual care". It was also assumed that the utility post-DBS holds when patients remain on DBS care.

When Romito 2015 was chosen to inform the model, the values 1-year and 2-years post-DBS were applied in the first and second year, whilst the value associated with the last visit was carried to a lifetime horizon.

There is a clear difference in pre-treatment utility between Vidailhet 2009 and Romito 2015, with participants in Romito 2015 entering the study with a much lower quality of life (0.35 vs. 0.61) (Table 28) most likely due to Romito 2015 only including patients with acquired dystonia (who may be less accustomed or have adapted to their condition) compared to Vidailhet which only included patients with idiopathic or inherited dystonia. For example, Vidailhet 2009 required optimum pharmacological treatments to be ineffective, whereas Romito 2015 did not specify this. In addition, it has been shown that mapping functions tend to overestimate utilities associated with severe health states and underestimate utilities associated with good health (Rowen 2009). For these reasons, the studies were not pooled and used separately in the model. However, it is evident that if DBS is not found to be cost-effective when Romito 2015 is used to inform the model, it will not be cost-effective according to Vidailhet 2009 who provides lower incremental QALY gains post- vs. pre- DBS.

People who undergo DBS experience some level of disutility due to the length and intensity of their inpatient stay, as DBS is an invasive and complex procedure. Despite this, no utility values in relation to the procedure were identified from the literature. Instead, the disutility was imputed using the EQ-5D health state valuation equation for the UK reported by Dolan 1997 which allows estimation of a person's utility based on their responses to the EQ-5D classification system. The system has 5 dimensions (mobility, self-care, ability to perform usual activities, pain/discomfort, and anxiety/depression) and in the version used by Dolan 1997, each dimension had 3 levels of response (no problems, moderate problems, and severe problems).

Only the utility decrement due to usual activities was applied as this was considered to be the most dependable dimension on the neurosurgical procedure. This disutility is expressed by the following equation:

$$Y = \alpha + UA + U2 + N3$$

Where:

- α = 0.081 (constant applied to any level of disutility in any of the 5 EQ-5D dimensions)
- UA = -0.036 (for each level of disutility associated with usual activities)
- U2 = -0.022 (for being unable to perform usual activities)
- N3 = -0.269 (when any of the 5 dimensions of EQ-5D is severe)

As the baseline utility for people with cerebral palsy in the model is less than 1 (perfect health) for both Romito 2015 (0.35) and Vidailheit 2009 (0.61) the α value was not applied at the estimation of the utility decrement. and they moved from a state of moderate problems to being unable to perform them. Also assuming that at least one other dimension was severe, the N3 value is not added again, resulting in a disutility of -0.094 (-0.036-0.036-0.022).

To reflect the length of the procedure, the disutility was applied for 2 weeks in the model - a QALY loss of -0.004 (-0.094*(2/52)).

Hardware-related failures also require surgery to correct. For this reason, a 1 week QALY loss -0.002 (-0.094*(1/52)) was applied to patients receiving surgical treatment to correct hardware-related failures.

DBS-related complications

Infection

The committee agreed that an infection would negatively impact a patient's quality of life, namely from the pain/discomfort infections can cause. As a result, a source for a disutility was sought, but in the absence of a relevant source, the method to estimate the disutility associated with the procedure was used by applying the dimension for pain/discomfort.

Where:

- α = 0.081 (constant applied to any level of disutility in any of the 5 EQ-5D dimensions)
- PD = -0.123 (for each level of disutility associated with pain/discomfort)
- P2 = -0.140 (for severe pain/discomfort)
- N3 = -0.269 (when any of the 5 dimensions of EQ-5D is severe)

As before, people with cerebral palsy already have a utility less than 1. Assuming that they moved from a state of no pain/discomfort to moderate pain/discomfort the resulting disutility is -0.123.

This disutility of -0.123 was applied for 2-weeks in the model, as pain/discomfort from an infection would be unlikely to last longer. This gave a 2-week QALY loss of -0.0047 (-0.123*(2/52)) attributed to pain/discomfort from an infection.

Seizure

A loss of -0.0014 was reported by Lee 2013 for a seizure (>10 minutes or repeated but not admitted). This value was estimated from the parents of children with epilepsy and a Delphi panel audit of clinicians in Wales for the treatment of prolonged acute convulsive seizures in children and adolescents.

Lee 2013 was the only relevant source identified to inform this input.

ICH

Lip 2015 estimated utilities for mild, moderate and severe ischemic or haemorrhagic strokes from a UK based utility catalogue of EQ-5D sores for the UK (Sullivan 2011). However, patients entered their cost-utility model at 70 years of age. To account for this, the health state utility decrement for ICH was estimated using the percentage reduction in utility when the utilities estimated by Lip 2015 are compared with EQ-5D population event-free norms (Kind 1999).

The percentage utility for a minor ICH was estimated by calculating the percentage change from the patient in Lip 2015 with a minor ICH (utility 0.6151) to a patient aged 65-74 years without a minor ICH (Kind 1999 utility 0.7800): 0.6151/0.7800 = 78.9%.

Similarly, the percentage utility for a major ICH was estimated by calculating the percentage change from the patient in Lip 2015 with a major ICH (utility 0.5142) to a patient aged 65-74 years without a minor ICH (Kind 1999 utility 0.7800): 0.5142/0.7800 = 65.9%.

Long-term ICH care

Begum 2015 considered the long-term effects of a haemorrhagic stroke/ICH in their cost-utility analysis by including a disutility for the subsequent cycles following a haemorrhagic stroke/ICH. Begum 2015 added, that their utility values taken from the Platelet inhibition and patient Outcomes (PLATO) trial were elicited from a large number of patients and had been applied in many recent heath technology appraisal submissions as a robust source.

The relative percentage utility for long-term ICH care in the model was estimated by calculating the percentage change from the patient in Begum 2015 with a long-term ICH (utility 0.792) to the baseline (event-free) utility they reported (0.842): 0.792/0.842 = 94.1%.

Table 29 summarises the disutilities applied in the model.

Table 29: Disutility from DBS-related complications

Complication	Duration	Disutility (QALY loss)	Source
Procedure	2 weeks	-0.094 (-0.004)	Dolan 1997 (usual activities)
Hardware	1 week	-0.094 (-0.002)	Dolan 1997 (usual activities)
Infection	2 weeks	-0.123 (-0.005)	Dolan 1997 (pain/discomfort)
Seizure	1 day	(-0.001)	Lee 2013
ICH minor	2 weeks	-21.1%	Lip 2015
ICH major	6 weeks	-34.1%	Lip 2015
Long-term ICH care	Lifelong	-5.9%	Begum 2015

QALY, quality-adjusted life year = quality of life x duration

A sensitivity analysis assuming no utility decrements was explored in the model as DBS-related complications can be minor. In addition, the methods used to estimate the disutility may overestimate the impact of the event given the lack of relevant quality of life data reported in the literature.

Mortality

Cerebral palsy-related

The committee considered Brook 2014 to provide up-to-date survival estimates for people with cerebral palsy living in California that would be generalisable to adults living in England and Wales.

Brook 2014 reported survival estimates for 5 levels of severity which enabled the model to select those levels appropriate for people with dyskinetic cerebral palsy. To select the appropriate levels, the committee agreed it would be reasonable to assume that GMFCS is stable and can be informed by paediatric data that assess GMFCS and learning disability in older children with dyskinetic cerebral palsy. Himmelmann 2007 described 48 participants with dyskinetic cerebral palsy in Western Sweden. Their gross motor function was classified according to the GMFCS and was subsequently transformed into the limitations by Brook 2014 to create a weighted average (Table 30).

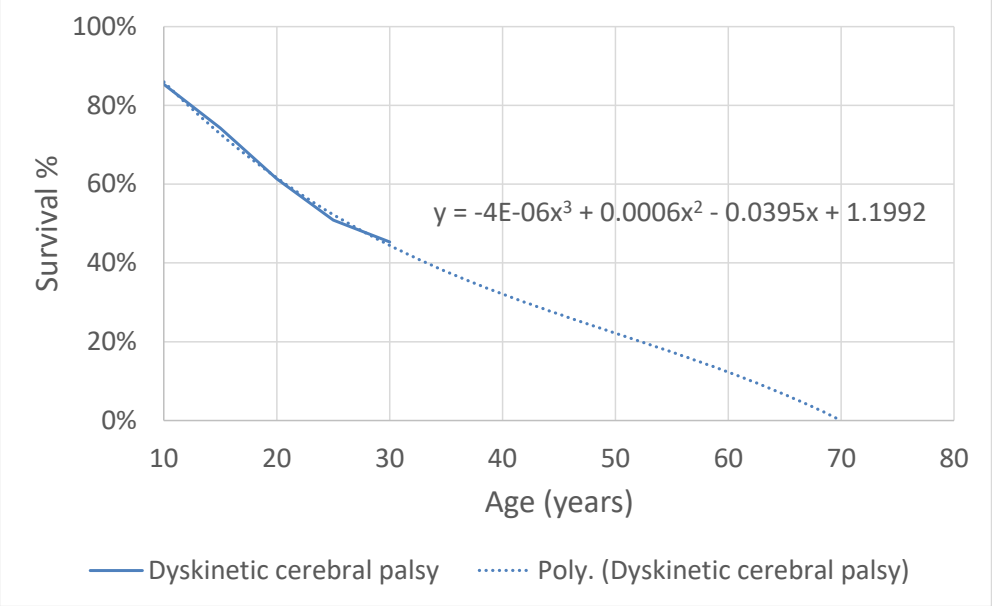
Table 30: GMFCS levels used to inform dystonic limitations

Brook 2014 limitations	GMFCS	Himmelmann 2007, n	%
Does not lift head in prone position	5	28	58%
Lifts head but not chest in prone position	4	10	21%
Lifts head and chest, partial rolling	3	6	13%
Full rolling, does not walk unaided	2	2	4%
Walks unaided	1	2	4%
Total	NA	48	100%

GMFCS: Gross motor function classification system

The probability a child with cerebral palsy will survive is reported up to the ages of 10, 15, 20, 25, and 30 years by Brook 2014. However, given that people with cerebral palsy are expected to live up to 70 years, the data beyond 30 years was extrapolated using a polynomial trend (Figure 17).

Figure 17: Survival



The committee agreed there was no evidence to suggest DBS treatment impacts survival following the procedure; hence, the same trend was applied to both treatment arms in the model.

DBS procedure

DBS is a risky and invasive procedure. The committee agreed that procedure-related mortalities reported in the literature were low, but concluded procedure-related mortality was an important possibility to capture in the model.

Boviastis 2010 reported a perioperative mortality of 0.94% in their study, whilst the literature review by Voges 2006 identified 1 study that reported mortality (Umemura 2003, 1.8%) with a similar rate. However, the remaining studies reviewed by Voges 2006 did not report mortality.

Major ICH

Gonzalez 2013 investigated short-term case fatality and long-term mortality after ICH using data from The Health Improvement Network (THIN) database over the years 2000 to 2008. A total of 1,733 individuals with an ICH and 9,583 controls were available with follow-up data.

Using logistic regression, event fatalities were stratified by age. For people aged 20 to 49 years Gonzalez 2013 estimated a 30-day case fatality of 29.7% for an ICH.

Cox proportional hazards regression analyses were used to determine whether patients were at increased risk of death in the first year (excluding the first 30 days immediately after the event) and after 1 year compared with the general population (controls) in THIN.

They found that the risk of death was significantly higher among stroke patients during the first year of follow-up compared with controls (HR 2.60, 95% CI 2.09–3.24) and remained elevated among survivors at 1 year (HR 2.02, 95% CI 1.75–2.32).

Resource and cost use

Deep brain stimulation (DBS)

Yianni 2005 provided a detailed cost-analysis of DBS surgery, including the preoperative assessment, surgery, equipment, postoperative management/follow-up and complications when they estimated cost-effectiveness. Costs were examined over a period of 2 years on 26 patients with primary dystonia. The effectiveness of DBS between primary dystonia and dystonic cerebral palsy will differ; hence, their estimate of cost-effectiveness was not considered to be relevant for this guideline.

However, the Committee agreed that the resources reported by Yianni 2005 would be very similar to those for dystonic cerebral palsy. Those costs are reproduced here in 2002/3 prices and 2015/16 prices using the hospital and community health services pay and prices index uplift (Curtis 2015) (Table 31).

Table 31: Cost of DBS reproduced from Yianni 2005

Cost component	Cost per patient, 2002/3	Cost per patient, 2015/16[a]
Preoperative assessment costs (consultation with a neurologist & 2-day inpatient stay with contact from a neuropsychologist)	£856	£1,190
Surgery (staff costs, theatre time (3 hours), ward stay (10 days), MRI, CT, ECG, chest X ray)	£6,115	£8,499
Stimulation equipment costs per surgical episode (Kinetra IPG, electrode lead, extension lead)	£11,104	£15,432
Localisation equipment (planning station, stereotactic frame)	£1,593	£2,214
Total cost of procedure	**£19,668**	**£27,335**
Monitoring per year (1 neurosurgery outpatient visit, 3 specialist nurse visits, 3 neurology outpatient visits)	£621	£863

CT: computerised tomography; ECG: electrocardiography; MRI: magnetic resonance imagining
(a) HSHC inflations factor 1.3898 (2015/16 PPI 297/ 2002/03 PPI 213.7)

The committee suspected that Yianni 2005 may not reflect the latest innovations in equipment, particularly with regards to the type of rechargeable battery now available. To account for this uncertainty, a tornado diagram was presented, varying the cost inputs by +/- 50%.

DBS-related complications

Replacement IPG

Yianni 2005 reported a cost of £8,356 (2015/16 cost: £11,613) to replace an IPG. According to the committee IPGs are usually replaced every 5 years. However, the committee also noted that the lifespan of an IPG is variable and could improve with innovations. To account for this, a replacement every 2 and 8 years was explored in sensitivity analysis.

Hardware-related

Yianni 2005 reported a cost of £11,169 (2015/16 cost: £15,523) to correct hardware failures. No further details on this estimate were provided.

Infection-related

Yianni 2005 reported a cost of £17,319 (2015/16 cost: £24,070) to manage infections. No further details on this estimate were provided, but the committee agreed that the high cost may include the cost to remove the DBS system.

Patients who remain on DBS following an infection, received antibiotics via intravenous infusion for 2 weeks at a cost of £560 (BNF August 2017: Ciprofloxacin 400 mg every 8–12 hours, £20.00 per infusion).

Seizure

A seizure would require a CT scan (NHS Reference Costs 2015/16: RD20A direct access, £99) and intravenous anticonvulsants such as diazepam (NHS Electronic Drug Tariff: 10mg/2ml solution for injection ampoules, £0.55/ampoule) to assess and manage.

Minor ICH

The cost of a minor ICH (£2,745) was taken from NHS Reference Costs 2015/16 using the code associated the lowest complications and comorbidity (CC) score (currency code: AA35F; currency description: stroke with CC score 0-3).

If patients experienced the ICH before their surgery was completed, the surgery would be abandoned and reversed at a 2015/16 cost of £8,499 (Yianni 2005).

Major ICH

The cost of a major ICH (£4,854) was taken from a weighted average of NHS Reference Costs 2015/15 that related to a stroke (currency codes AA35A:AA35F) to incorporate complex and costly strokes associated with complications and comorbidities.

DBS equipment would be removed following a major ICH at a cost of £8,499 (Yianni 2005) based on the assumption that all major ICHs occurred near or after complete surgery.

According to NICE CG92 and NICE CG68 long-term ICH care would cost £4,826 per year to manage (£4,826 x [2015/16 PPI 297.0/ 2009/10 PPI 268.6] = £5,336).

Usual care

In the base case, patients received trihexyphenidyl (5mg daily) to align with the type of pre-treatment participants received in Vidailhet 2009 and Romito 2015 and the type of pharmacological treatment used in clinical practice today (Table 32). Patients receiving trihexyphenidyl visit a neurologist each year to monitor their response at a cost of £161 (NHS Reference Costs 2015/16, currency code WF01A, service code 400, non-admitted face-to-face attendance follow-up, neurology).

Table 32: Cost of usual care (trihexyphenidyl)[a]

Drug	Quantity	Basic price	Cost per tablet	Cost per year (5mg daily)
Trihexyphenidyl 5mg tablets	84	£17.91	£0.21	£77.82

[a] *NHS Electronic Drug Tariff August 2016*

A sensitivity analysis administering botulinum toxin every 6 months was also explored as a sensitivity analysis. Botulinum toxin involves a day–case admission performed by a neurologist, rehabilitation medicine doctor, or a specially trained physiotherapist or nurse in a specialist clinic. Adults with cerebral palsy are unlikely to be sedated, but ultrasound or electromyography may be used for guidance. However, given that recommendations were

not included on ultrasound or electromyography guidance, they are not added here for consistency.

The appointment for the injection of botulinum has a NHS reference cost assigned – Torsion dystonia and other involuntary movements drugs band 1 (code XD09Z). This reference cost (£324) will include all costs related to the procedure, the day case admission, drug costs and staff costs.

Following the injections, patients would be monitored every 3 to 4 months by the specialist clinic at a cost of £161 (NHS Reference Costs 2015/16, currency code WF01A, service code 400, non-admitted face-to-face attendance follow-up, neurology) to assess their response and need for repeat injections.

Sensitivity analysis

A series of sensitivity analyses were undertaken in order to test how sensitive the results were to uncertainty in individual parameters. Parameters varied in sensitivity analysis were chosen on the basis of uncertainty in their estimation or the potential impact that they had on the results. Extreme analysis were reported when smaller changes in those analysis led to negligible differences in the results. For example, changing all utility decrements to zero instead of a single utility decrement. The values varied, along with their rationale are shown in Table 33.

Table 33: Description of sensitivity analysis

SA: parameter to be changed	Default value	Value tested	Rationale
1 Replacement IPG	5 years	2 and 8 years	The lifespan of an IPG is variable and may improve with innovations. The results of this are presented in a tornado diagram.
2 Disutility associated with DBS-related complications	Table 29	0	Complications can be minor and relatively short and may not negatively impact on quality of life
3 Probability of DBS-related complications	Table 24	0	The probability of DBS-related complications depends on the experience of the HCPs performing the procedure and not all complications of DBS were experienced by departments
4 Time horizon	Lifetime	Within-trial	The utility values obtained at the last visit may not be reflective of utility in years to come
5 Treatment received in usual care	Trihexyphenidyl	Botulinum toxin	Patients who are eligible for DBS could receive botulinum toxin which is more costly, reducing the incremental cost of DBS.
6 Cost of DBS procedure	**Error! Reference source not found.**	+/- 50%	The cost of DBS reported by Yianni 2005 will not incorporate the latest innovations and experience in the procedure that could reduce the cost. The results of this are presented in a tornado diagram.
7 Cost to treat complications		+/- 50%	The cost of some complications was taken from Yianni 2005 who provided little detail regarding their cost build-up. Moreover, the severity of complications and their treatment can vary. The results of this are presented in a tornado diagram.

DBS: Deep Brain Stimulation; HCP: healthcare practitioner; IPG: implantable pulse generator.

Probabilistic sensitivity analysis (PSA) was conducted in the model to take account of the simultaneous effect of uncertainty relating to model parameter values. Key parameters in the model relating to clinic effectiveness were varied by sampling from probability distributions. The model was run for 1,000 simulations to generate estimates of total costs and total QALYs by varying those parameters simultaneously. The model structure and model settings were kept constant. Cost parameters were not varied in PSA as the cost of equipment, drugs and monitoring related to the interventions were expected to be fixed. Disutility values associated with complications were not varied as their distributions around the mean could not be calculated for all complications, and given the small decrement associated with those complications, this was a minor omission. As previously stated, cost inputs were varied in sensitivity analysis using +/-50% of the base case value.

Table 34: PSA parameters

Parameter	Dist.	Mean	SD	Source(s)
Utility				
Vidailhet 2009 pre-DBS	Beta	0.61	0.08	Vidailhet 2009/ Ara & Brazier 2008
Vidailhet 2009 1-year post-DBS	Beta	0.72	0.07	Vidailhet 2009/ Ara & Brazier 2008
Romito 2015 pre-DBS	Beta	0.35	0.06	Romito 2015/ Ara & Brazier 2008
Romito 2015 1-year post-DBS	Beta	0.61	0.06	Romito 2015/ Ara & Brazier 2008
Romito 2015 2-years post-DBS	Beta	0.65	0.07	Romito 2015/ Ara & Brazier 2008
Romito 2015 last visit	Beta	0.66	0.06	Romito 2015/ Ara & Brazier 2008
Complications				
Hardware-related	Beta	0.040	0.042	Mean and SD from a weighted average of Bovistis 2010 and the studies included in the review by Voges 2006
Infection-related (first cycle only) [a]	Beta	0.015	0.012	Mean: Voges 2006 SD using a weighted average with Bovistis 2010
Seizure	Beta	0.094	0.008	Mean: Bovistis 2010 SD using a weighted average of the studies in Voges 2006
Minor ICH	Beta	0.027	0.015	Mean: Binder 2005 SD using a weighted average of the studies in Voges 2006
Major ICH	Beta	0.006	0.015	Mean: Binder 2005 SD using a weighted average of the studies in Voges 2006
Procedure-related mortality	Beta	0.094	0.009	Mean: Bovistis 2010 SD using a weighted average of the studies in Voges 2006
Infection-related (second cycle)	Beta	0.061	0.006	Mean: Voges 2006 SD using +/-20% of the mean in the absence of the evidence of dispersion
Switch to usual care (Trihex) following infection	Beta	0.800	0.082	Mean: Binder 2005 SD using +/-20% of the mean in the absence of the evidence of dispersion

Parameter	Dist.	Mean	SD	Source(s)
Switch to usual care (Trihex) following minor ICH	Beta	0.230	0.023	Mean: Binder 2005 SD using +/-20% of the mean in the absence of the evidence of dispersion

DBS: Deep Brain Stimulation; Dist.: distribution; ICH: intracranial haemorrhage; SD: standard deviation

4. The timing of infections was not reported sufficiently in the studies to estimate a probabilistic value for the second cycle, or for the transitions following an infection

Results

As discussed previously, the results for Vidailhet 2009 and Romito 2015 are presented separately due to study heterogeneity. The total costs for each intervention are the same for each study as the studies only vary in the utility data they provide.

Study participants in Vidailhet 2009 had a greater utility pre- and post- DBS treatment compared to Romito 2015 (pre-DBS: 0.61 vs. 0.35; post-DBS: 0.72 vs. 0.66). As a result, the total QALYs are much higher when Vidailhet 2009 is used to inform the model. Moreover, study participants in Romito 2015 had more potential to benefit from DBS treatment with a much greater improvement in their utility value pre- vs. post-DBS treatment (0.66 - 0.35 = 0.31). Therefore, if DBS is not found to be cost-effective when Romito 2015 is used to inform the model, DBS will not be cost-effective according to Vidailhet 2009 who has less favourable incremental utility data pre- vs. post- DBS.

Base case results

When Romito 2015 was used to inform the model, DBS was more costly and more effective than usual care, with an ICER on NICE's lower threshold (Table 35). This is illustrated in Figure 18 with an ICER in the north-east quadrant.

DBS was also more costly than usual care according to Vidailhet 2009, but relatively less effective than Romito 2015. As a result, the ICER was higher when Vidailhet 2009 was used to inform the model.

It is important to note that Vidailhet 2009 produced more QALYs than Romito 2015 because Vidailhet 2009 reported higher utility values pre- and post-DBS treatment (Table 35).

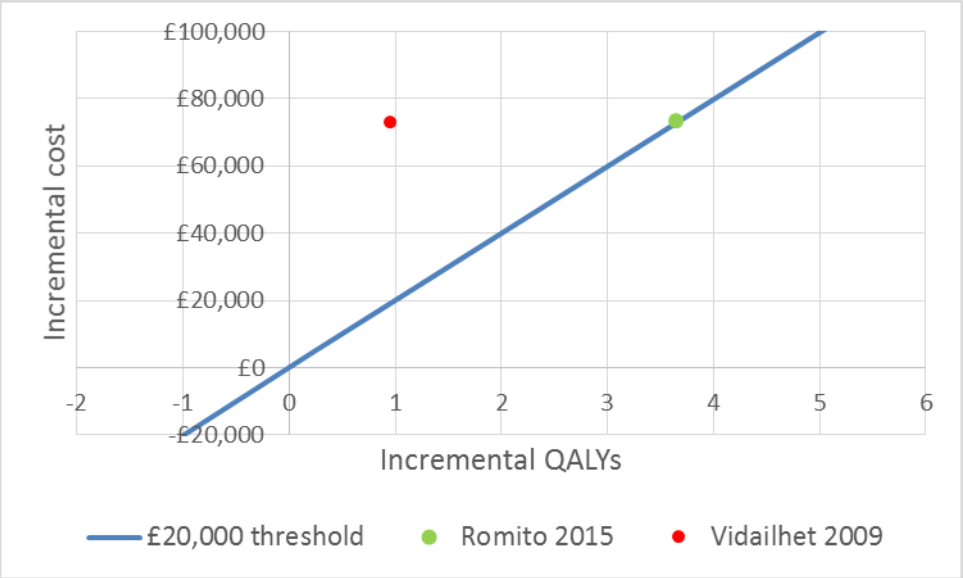
However, as stated above, the range is greater for Romito 2015. The total costs do not differ between the studies as they only differ in utility values.

Table 35: Base case results (deterministic)

	Total costs	Total QALYs	ICER
Vidailhet 2009			
Usual care	£3,464	8.87	
DBS	£76,991	9.82	£77,181
Romito 2015			
Usual care	£3,464	5.01	
DBS	£76,991	8.66	£20,169

DBS: Deep Brain Stimulation; ICER: Incremental cost effectiveness ratio; QALY: Quality-adjusted life year.

Figure 18: Cost-effectiveness plane (base case)



Sensitivity analysis results

The total QALYs increased for DBS when utility decrements were removed and when the risk of complications were removed. This reduced the ICER for Vidailhet 2009 and Romito 2015, but the ICER for Vidailhet 2009 remained above NICE's upper threshold of £30,000 per QALY.

Reducing the time horizon reduced the number of QALYs that could be accrued and amplified the cost of the DBS procedure. This analysis increased the ICER above NICE's upper threshold in both studies.

When usual care consisted of botulinum toxin (a more costly treatment than trihexyphenidyl) the incremental cost reduced. This reduced the ICER for Vidailhet 2009 and Romito 2015, but the ICER for Vidailhet 2009 remained above NICE's upper threshold of £30,000 per QALY.

The results of each analysis are provided in Table 36 for Romito 2015 and Table 37 for Vidailhet 2009.

Table 36: Results of sensitivity analysis (Romito 2015)

	Total costs	Total QALYs	ICER
Disutility associated with DBS-related complications set to 0			
Usual care	£3,464	5.01	-
DBS	£76,991	8.66	£20,157
Probability of DBS-related complications set to 0			
Usual care	£3,464	5.01	-
DBS	£70,097	9.13	£16,163
Time horizon 4 years			
Usual care	£1,075	1.56	-
DBS	£40,995	2.80	£32,193
Treatment received in usual care (Botulinum)			
Usual care	£17,572	5.01	-
DBS	£78,081[a]	8.66	£16,598

DBS: Deep Brain Stimulation; ICER: Incremental cost effectiveness ratio; QALY: Quality-adjusted life year.
5. Cost higher than the base case as some complications lead people to switch from DBS to usual care

Table 37: Results of sensitivity analysis (Vidailhet 2009)

	Total costs	Total QALYs	ICER
Disutility associated with DBS-related complications set to 0			
Usual care	£3,464	8.87	-
DBS	£76,991	9.83	£76,953
Probability of DBS-related complications set to 0			
Usual care	£3,464	8.87	-
DBS	£70,097	10.07	£55,610
Time horizon 4 years			
Usual care	£1,075	2.75	-
DBS	£44,956	3.07	£137,126
Treatment received in usual care (Botulinum)			
Usual care	£17,572	8.87	-
DBS	£78,081[a]	9.82	£63,516

DBS: Deep Brain Stimulation; ICER: Incremental cost effectiveness ratio; QALY: Quality-adjusted life year.
(c) Cost higher than the base case as some complications lead people to switch from DBS to usual care

Figure 19 illustrates the ICERs for Romito 2015 when each component of the procedure was varied using half the cost of the base case (-50%) and 150% of the base case (+50%). In the worst case scenario, increasing the cost of the total procedure by 50% increased the ICER to £23,918. In the best case scenario, reducing the total cost of the procedure by 50% reduced the ICER to £16,420.

Figure 20 also used this method to show the variability in ICERs to treat the complications of DBS for Romito 2015. The most influential parameters were related to the replacement of the IPG. When the cost to replace the IPG was varied by 50% the ICER ranged from £16,456 to £23,873. When the frequency of replacements was changed from every 5 years to every 2 or 8 years, the ICER ranged from £16,884 to £33,474.

Figure 19: Tornado diagram of the costs associated with the procedure and monitoring (Romito 2015)

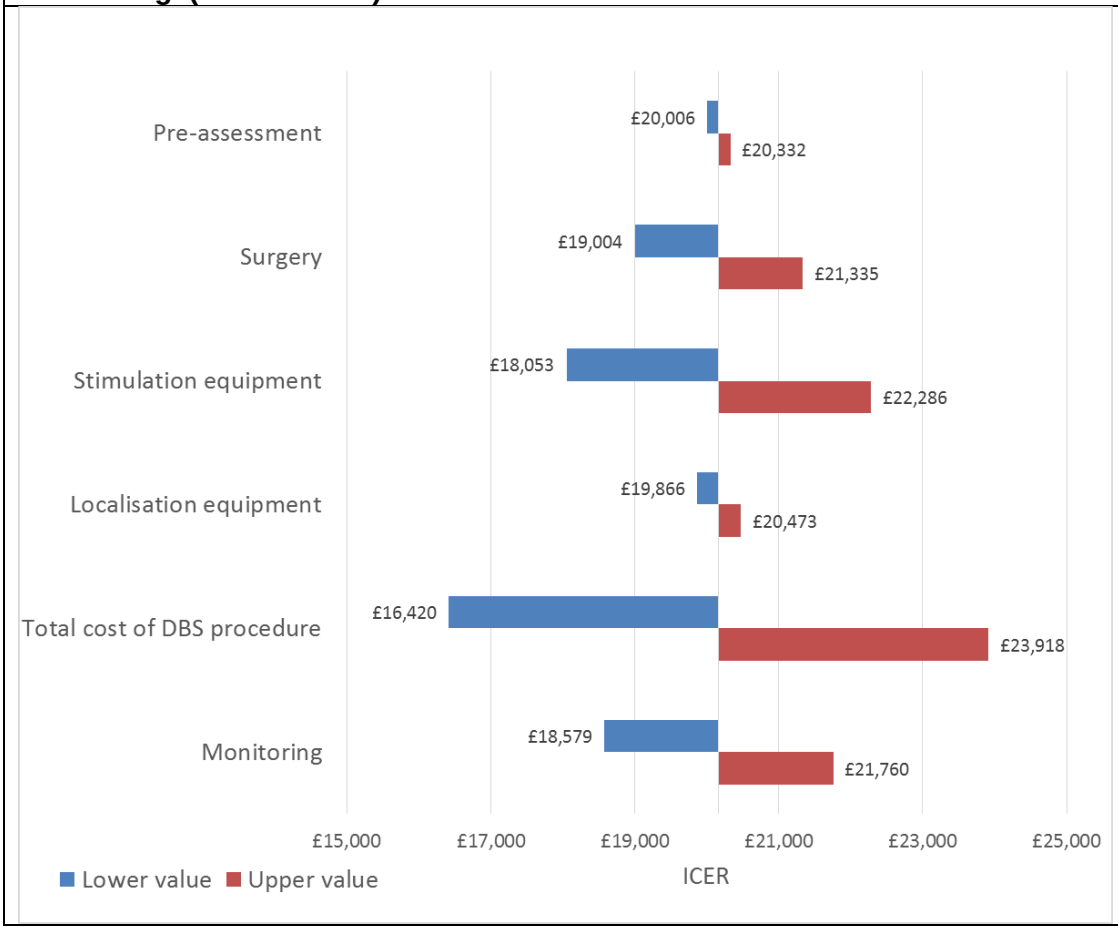


Figure 20: Tornado diagram of the costs to treat the complications of DBS (Romito 2015)

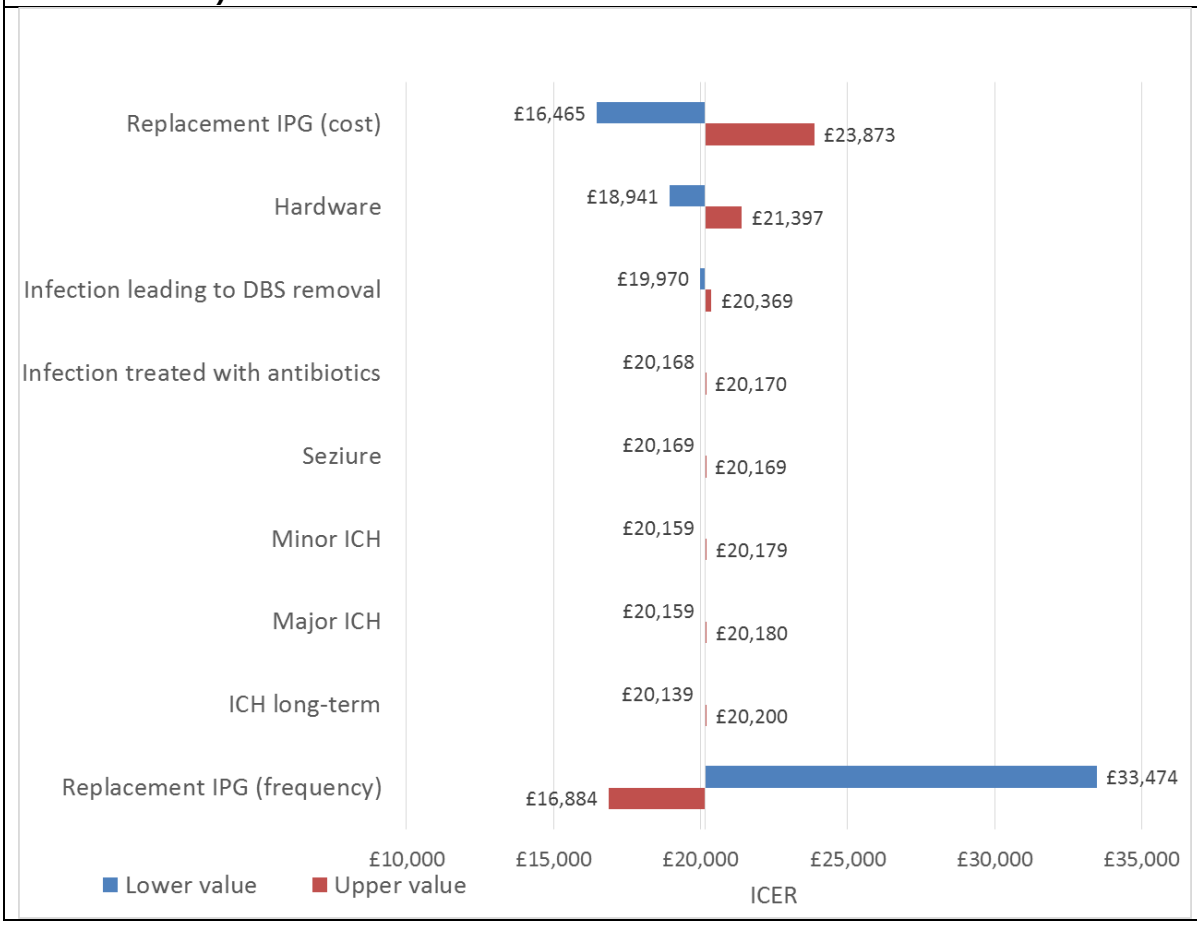
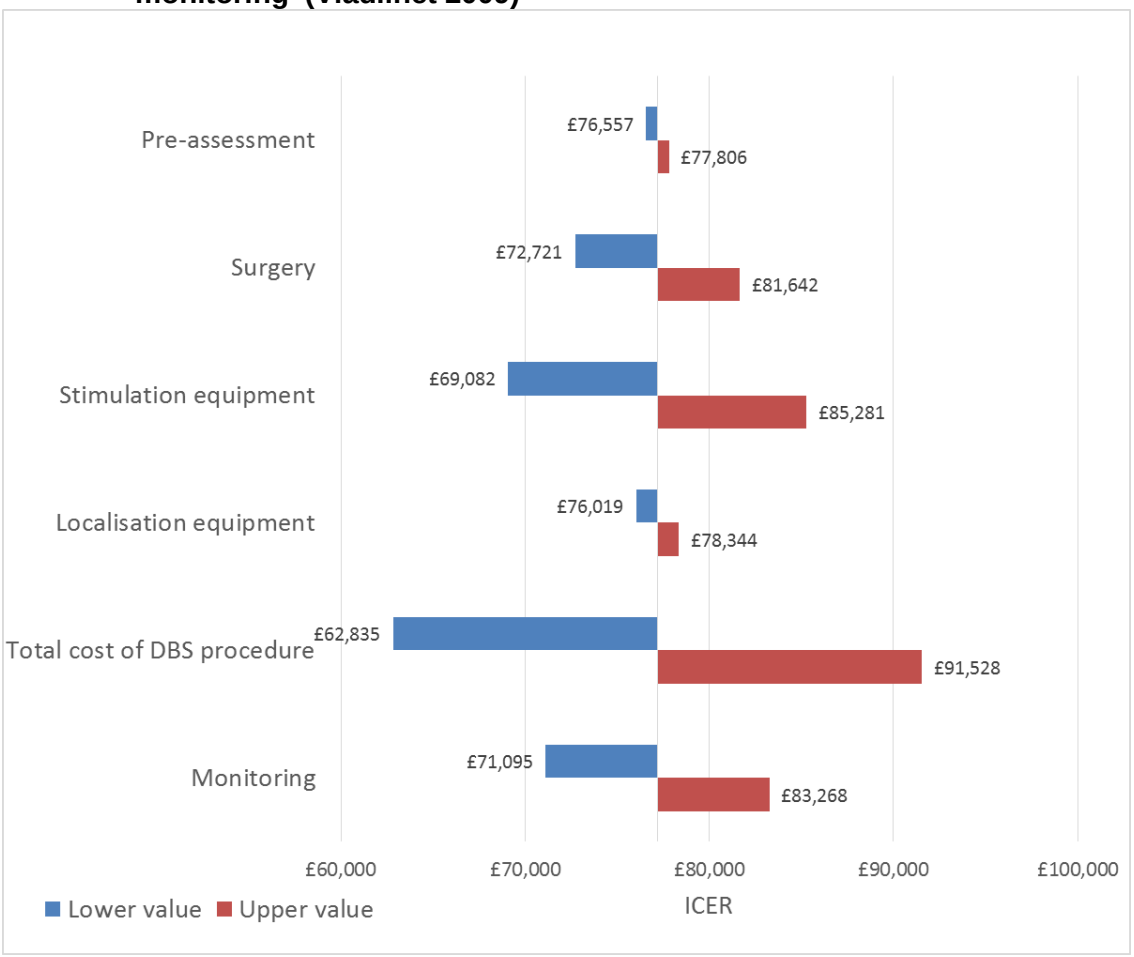


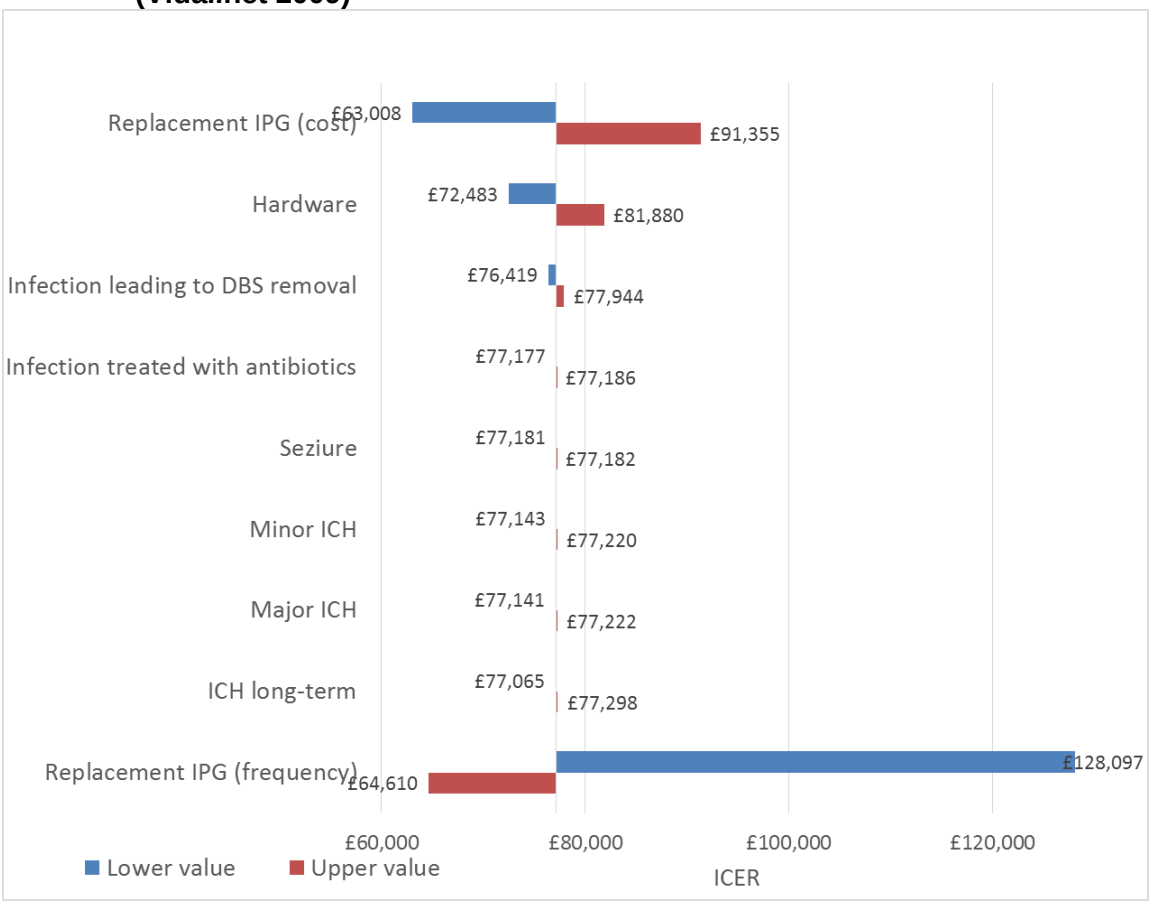
Figure 21 illustrates the ICERs for Vidailhet 2009 when each component of the procedure was varied using half the cost of the base case (-50%) and 150% of the base case (+50%). Figure 22 also used this method to show the variability in ICERs to treat the complications of DBS for Vidailhet 2009. All ICERs remained above NICE's upper threshold when those parameters were varied. Similarly to Romito 2015, the most influential parameters included the total cost of the procedure (namely stimulation equipment) and IPG replacements.

Figure 21: Tornado diagram of the costs associated with the procedure and monitoring (Viadilhet 2009)



1

Figure 22: Tornado diagram of the costs to treat the complications of DBS (Vidailhet 2009)



Probabilistic results

For Romito 2015, all simulations found DBS to be more effective and more expensive than usual care with a mean probabilistic ICER of £20,077. Furthermore, 739 of 1,000 simulations had ICER's below £20,000 and 927 below £30,000. This is illustrated in Figure 23where simulations cross the WTP threshold in the north-east quadrant. The simulations do not fall below an incremental cost of £60,000 as the cost inputs were not sampled. For this reason, the incremental cost cannot fall below the cost to provide DBS.

The cost-effectiveness acceptability curve (CEAC) also illustrated that DBS would be considered as the most optimal treatment for WTP thresholds over £17,000 (Figure 24).

Figure 23: PSA simulations (Romito 2015)

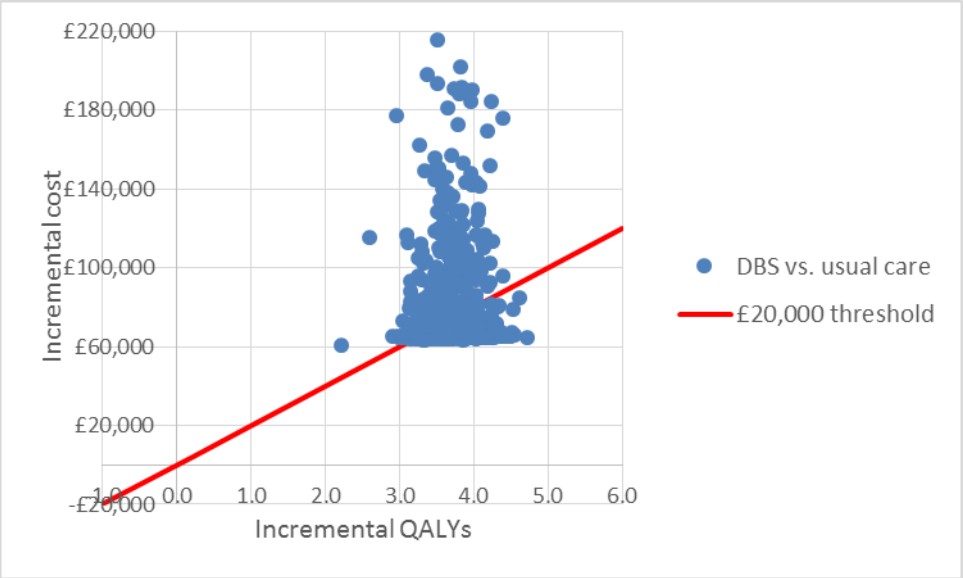
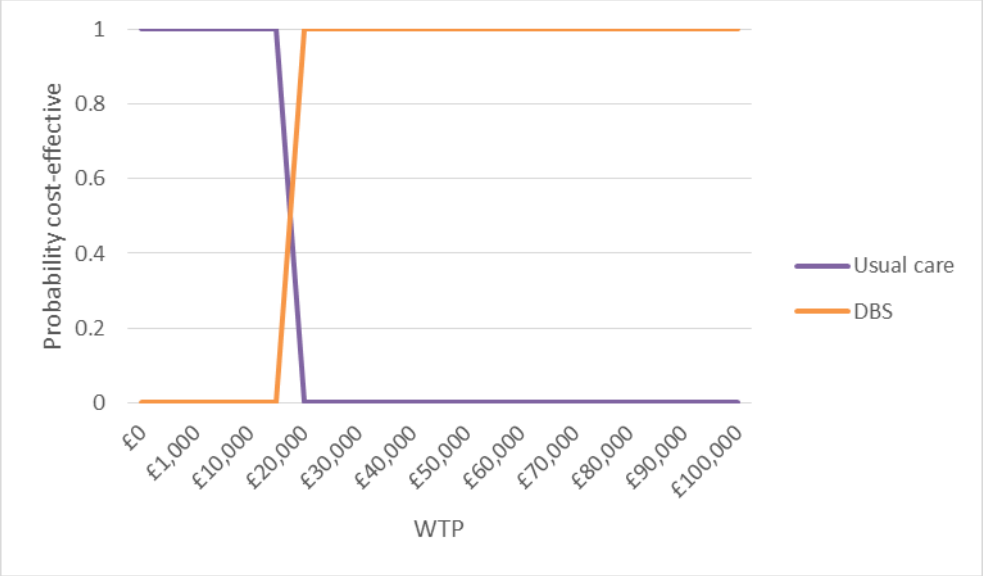


Figure 24: CEAC (Romito 2015)



When Vidailhet 2009 was used to inform the model, the mean ICER was £72,323 with almost all simulations (996 of 1,000) in the north-east quadrant above NICE's threshold (Figure 25). The CEAC also illustrated that usual care would be considered as the most optimal treatment for WTP thresholds up to £65,000 per QALY (Figure 26).

Figure 25: PSA simulations (Vidailhet 2009)

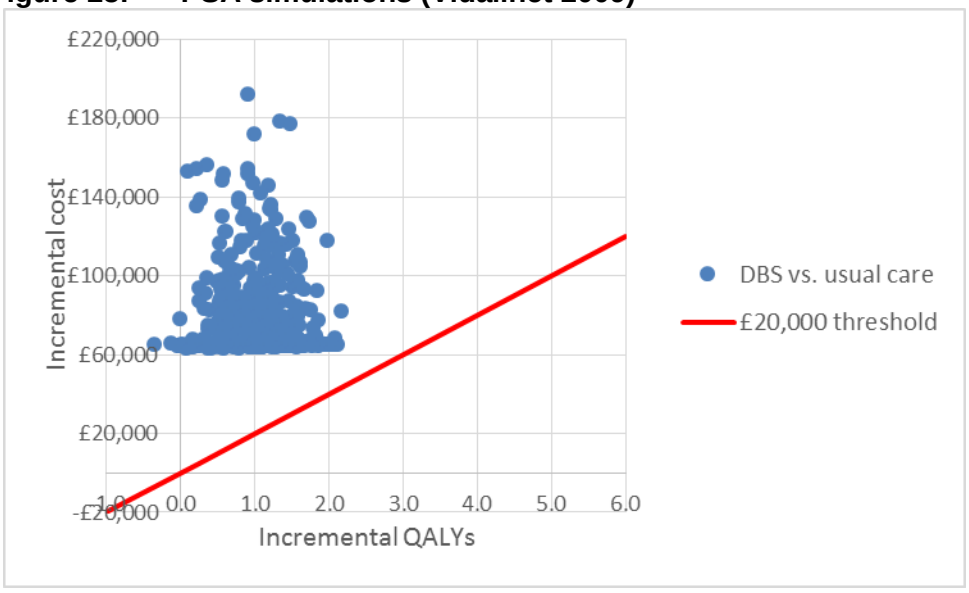


Figure 26: CEAC (Botulinum toxin)

Discussion

This is the first cost-effectiveness analysis of DBS to manage dystonia in adults with cerebral palsy. Using QALYs, as the measure of effectiveness, incorporates changes in morbidity and mortality and allows broad comparisons across all health care interventions provided by the NHS. In addition, undertaking cost-utility analysis was of upmost importance, given the need to assess the trade-offs from various treatment related adverse events, complications and failures.

The economic model developed for this review was based on committee opinion regarding current treatment pathways and the plausibility of relationships between complications and their subsequent consequences.

The model was informed by 2 before-and-after type studies in the absence of higher quality studies such as randomised controlled trials. The utility pre-DBS in those 2 studies that were

included was used as a proxy for usual care based on the assumption that if DBS was not available, participants would stay on the same treatment schedule. It is also important to note that the utility post-DBS may double count adverse events if a number of participants experienced them. However, the adverse events reported by the studies were relatively minor and potentially unrelated to DBS.

In clinical practice, a patient would not undergo an expensive, invasive and risky procedure such as DBS if pharmacological treatment effectively managed their dystonia. As a result, it is those patients for whom pharmacological treatment is ineffective where DBS would be considered. For these reasons, it is important for studies to state their inclusion criteria and the aims of treatment to know if we are comparing successful pharmacological treatment with DBS, or failed pharmacological treatment with DBS as the QALY gain would be very different for a pharmacologically successfully treated patient and one for which pharmacological treatment failed.

Some participants remained on pharmacological treatment after DBS at a lower dose in Vidailhet 2009 and Romito 2015. A simplifying assumption was made in the model that people would discontinue pharmacological treatment for dystonia after DBS. Drugs for dystonia are relatively cheap and could be monitored during routine reviews for DBS. So whilst this assumption may underestimate the cost of DBS even if these treatments were used over the lifetime of the patient the impact would be negligible and very unlikely to change conclusions.

The trials included in the clinical evidence review began DBS much later than the 19 years of age assumed by this economic evaluation. Given the models assumptions around survival it would overestimate the QALYs gained from treatment if it was initiated at a later age. However, the committee considered the inclusion criteria in the trials and concluded that age was independent of eligibility.

There was concern that the outcomes of DBS may be misrepresented by the studies, since the data was based on small numbers of participants. Due to such sparse evidence, it is clear more research on DBS is needed to increase confidence in its effects.

There is a potential publication bias, in that most studies are led by neurosurgeons and therefore, neuropsychiatric adverse events such as suicidal ideation, cognitive impairment or hallucinations, and more subtle physical adverse events may not be looked for. As a result the committee may want to consider a recommendation for specialists offering DBS to collect information on those short- and long-term outcomes with agreed consistent definitions.

The probability of failure and cost of DBS will be impacted on by whether the DBS implantation is image guided versus microelectrode recording guided, awake versus asleep, the programme used and bipolar versus monopolar stimulation, which also affects IPG battery life. Unfortunately, the studies on DBS used to inform the inputs in this model varied in this level of detail. As a result, the exact method of surgery is not defined in the model. However, this is not considered to be a severe limitation as the model was informed by a number of studies that reported the probability of DBS-related complications. Additional analysis varying the cost of treatment by +/-50% also assessed the impact on costs.

An important assumption in the model included extrapolation of the trial data to a lifetime horizon. On the one hand, this was useful to assess all important differences in costs and outcomes that would be possible from lifetime treatment and any potential complications. However on the other, it could potentially be misleading if the treatment effect is time dependent and could reduce the cost-effectiveness of DBS if effects reduced with time. To account for this uncertainty, the time horizon in the model could be varied.

Conclusion

DBS is more effective but also more costly than usual care according to Romito 2015 and Vidalhet 2009. When the ICER is considered the 2 studies lead to conflicting decisions around cost effectiveness. DBS could be considered cost effective according Romito 2015, which produces an ICER below NICE's advisory threshold of £20,000. Conversely, Vidailhet 2009 produces ICERs above £30,000 and would not be considered cost effective under conventional criteria.

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Himmelmann K, Hagberg G, Wiklund LM, Eek MN, Uvebrant P. Dyskinetic cerebral palsy: a population-based study of children born between 1991 and 1998. Dev Med Child Neurol. 2007 Apr;49(4):246-51.

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1 Appendix K – Excluded studies

2 Clinical and economic lists of excluded studies for review question A3: Which treatments
3 (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections),
4 neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing
5 dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?

6 Clinical studies

7 **Table 38: Excluded clinical studies for interventions for dystonia**

Excluded studies - A.3 Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?	
Study	**Reason for Exclusion**
Beecham, E., Candy, B., Howard, R., McCulloch, R., Laddie, J., Rees, H., Vickerstaff, V., Bluebond-Langner, M., Jones, L., Pharmacological interventions for pain in children and adolescents with life-limiting conditions, Cochrane Database of Systematic Reviews, 3, CD010750, 2015	Systematic review but in children-includes Bonouvrie 2011 and Hoving 2007 intrathecal baclofen trials
Berweck, S., BP-DBS for dystonia-choreoathetosis cerebral palsy, Lancet Neurology, 8, 692-693, 2009	Editorial on Vidailhet 2009
Bonouvrie, L. A., Becher, J. G., Vles, J. S. H., Boeschoten, K., Soudant, D., de Groot, V., van Ouwerkerk, W. J. R., Strijers, R. L. M., Foncke, E., Geytenbeek, J., van de Ven, P. M., Teernstra, O., Vermeulen, R. J., Intrathecal baclofen treatment in dystonic cerebral palsy: A randomized clinical trial: The IDYS trial, BMC Pediatrics, 13, 2013	Trial protocol for IDYS RCT
Bonouvrie, L., Becher, J., Soudant, D., Buizer, A., Van Ouwerkerk, W., Vles, G., Vermeulen, R. J., The effect of intrathecal baclofen treatment on activities of daily life in children and young adults with cerebral palsy and progressive neurological disorders, European Journal of Paediatric Neurology, 20, 538-544, 2016	No measurements before ITB - patients/carers asked to recall the situation before ITB pump
Boyd, Rn, Dobson, F, Parrott, J, Love, S, Oates, J, Larson, A, Burchall, G, Chondros, P, Carlin, J, Nattrass, G, Graham, Hk, The effect of botulinum toxin type A and a variable hip abduction orthosis on gross motor function: a randomized controlled trial, European Journal of Neurology, 8 Suppl 5, 109-19, 2001	Not dystonia, age 1-4 yrs
Butler,C., Campbell,S., Evidence of the effects of intrathecal baclofen for spastic and dystonic cerebral palsy, Developmental Medicine & Child Neurology, 42, 634-645, 2000	Systematic review, outdated - includes Albright 1996
Cif, A. L., Biolsi, B., Robles, S. G., El Fertit, H., Tancu, C., Vasquez, X., Coubes, P., Internal globus pallidus stimulation in the treatment of dystonic and dyskinetic syndromes associated with cerebral palsy, European Journal of Neurology, 13, 74-74, 2006	Abstract only - reports mean improvement in Burke Fahn Marsdenâ▼™s Dystonia Rating Scale
Cif, L., Deep brain stimulation in dystonic cerebral palsy: for whom and for what?, European Journal of Neurology, 22, 423-425, 2015	Editorial on Romita study
Cif, L., Martinez, V. G., Sanrey, E., Nerrant, E., Ros, M., Cyprien, F., Seng, E. C., Roujeau, T., Coubes, P., Axial prominent, delayed onset dystonia in cerebral palsy: Highlights on a distinct phenotype with favorable outcome following deep brain	Abstract only, case series (N=5)

Excluded studies - A.3 Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?	
Study	**Reason for Exclusion**
stimulation, Movement Disorders, 31, S561-S561, 2016	
Coelho, M., Cattoni, B., Lobo, P. P., Carvalho, H., Guedes, L. C., Sousa, P. R., Grunho, M., Albuquerque, L., Pereira, J. M., Reimao, S., Morgado, C., Ferreira, J. J., Rosa, M. M., Ferreira, A. G., Deep brain stimulation for the treatment of primary dystonias and dyskinetic cerebral palsy, European Journal of Neurology, 19, 678-678, 2012	Abstract only, case series (N=5)
Eltahawy, H. A., Saint-Cyr, J., Giladi, N., Lang, A. E., Lozano, A. M., Primary dystonia is more responsive than secondary dystonia to pallidal interventions: outcome after pallidotomy or pallidal deep brain stimulation, Neurosurgery, 54, 613-19; discussion 619-21, 2004	Not cerebral palsy
Gaasterland, C. M. W., Jansen-van der Weide, M. C., Weinreich, S. S., van der Lee, J. H., A systematic review to investigate the measurement properties of goal attainment scaling, towards use in drug trials, BMC Medical Research MethodologyBMC Med Res Methodol, 16, 2016	Systematic review of trials using goal attainment scales as outcomes
Katsakiori,P.F., Kefalopoulou,Z., Markaki,E., Paschali,A., Ellul,J., Kagadis,G.C., Chroni,E., Constantoyannis,C., Deep brain stimulation for secondary dystonia: results in 8 patients, Acta Neurochirurgica, 151, 473-478, 2009	N=2 patients with cerebral palsy
Kerr, C, McDowell, B, Cosgrove, A, Walsh, D, Bradbury, I, McDonough, S, Electrical stimulation in cerebral palsy: a randomized controlled trial, Developmental Medicine and Child Neurology, 48, 870-6, 2006	neuromuscular electrical stimulation, age < 16 years
Kerr, C., McDowell, B., McDonough, S., Electrical stimulation in cerebral palsy: A review of effects on strength and motor function, Developmental Medicine and Child Neurology, 46, 205-213, 2004	Systematic review of neuromuscular electrical stimulation
Kim, J. P., Chang, W. S., Chang, J. W., Treatment of secondary dystonia with a combined stereotactic procedure: long-term surgical outcomes, Acta Neurochirurgica, 153, 2319-27; discussion 2328, 2011	Combines DBS with unilateral thalamotomy
Koy, A., Hellmich, M., Pauls, A. M., Marks, W. A., Lin, J. P., Fricke, O., Timmermann, L., The effect of deep brain stimulation on cerebral palsy: A meta-analysis, Movement Disorders, 27, S318-S318, 2012	Systematic review - does not report by age subgroups. Checked for relevant studies.
Lannin, N. A., Novak, I., Cusick, A., A systematic review of upper extremity casting for children and adults with central nervous system motor disorders, Clinical Rehabilitation, 21, 963-76, 2007	Systematic review= no studies of adults with CP
Lettieri, C., Rinaldo, S., Devigili, G., Pisa, F., Mucchiut, M., Belgrado, E., Mondani, M., D'Auria, S., Ius, T., Skrap, M., Eleopra, R., Clinical outcome of deep brain stimulation for dystonia: Constant-current or constant-voltage stimulation? A non-randomized study, European Journal of Neurology, 22, 919-926, 2015	Mixed population of primary and other dystonia - cerebral palsy not reported.
Marks, W., Honeycutt, J., Acosta, F., Bailey, L., Reed, M., Pomykal, A., Mercer, M., Pallidal Stimulation Improves Dystonia in Cerebral Palsy, Neurology, 76, A330-A331, 2011	Abstract only - See Marks 2011 for full text
McGinley, J., Dobson, F., Morgan, P., A systematic review of the effect of interventions on gait in adults with cerebral palsy,	Systematic review - interventions not in protocol (more relevant for

Excluded studies - A.3 Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?	
Study	**Reason for Exclusion**
Developmental Medicine and Child Neurology, 54, 45-46, 2012	topic D2)
Merrill,D.R., Review of electrical stimulation in cerebral palsy and recommendations for future directions, Developmental Medicine and Child Neurology, 51, 154-165, 2009	Review of neuromuscular electrical stimulation
Mueller, J., Skogseid, I. M., Benecke, R., Kupsch, A., Trottenberg, T., Poewe, W., Schneider, G. H., Eisner, W., Wolters, A., Muller, J. U., Deuschl, G., Pinsker, M. O., Roeste, G. K., Vollmer-Haase, J., Brentrup, A., Krause, M., Tronnier, V., Schnitzler, A., Voges, J., Nikkhah, G., Vesper, J., Naumann, M., Volkmann, J., Pallidal deep brain stimulation improves quality of life in segmental and generalized dystonia: Results from a prospective, randomized sham-controlled trial, Movement Disorders, 23, 131-134, 2008	Primary dysonia
Naumann, M., Jankovic, J., Safety of botulinum toxin type A: a systematic review and meta-analysis, Current Medical Research and Opinion, 20, 981-990, 2004	Systematic review - some studies were in cerebral palsy but the age of participants and indication for botox not reported.
Pin, T. W., McCartney, L., Lewis, J., Waugh, M. C., Use of intrathecal baclofen therapy in ambulant children and adolescents with spasticity and dystonia of cerebral origin: a systematic review, Developmental Medicine & Child Neurology, 53, 885-95, 2011	Systematic review- found no studies on the use of ITB in children/adolescents with dystonia of cerebral origin
Romito, L. M., Zorzi, G., Ciceri, M. L., Marras, C. E., Franzini, A., Nardocci, N., Albanese, A., Long-term follow-up of GPi deep brain stimulation in generalized dystonia: Primary dystonia compared to cerebral palsy, Movement Disorders, 28, S434-S434, 2013	Abstract only - see Romito 2015
Schjerling, L., Hjermind, L. E., Jespersen, B., Madsen, F. F., Brennum, J., Jensen, S. R., Lokkegaard, A., Karlsborg, M., A randomized double-blind crossover trial comparing subthalamic and pallidal deep brain stimulation for dystonia: Clinical article, Journal of Neurosurgery, 119, 1537-1545, 2013	Primary dystonia or secondary to medication.
Sokal, P., Rudas, M., Harat, M., Szylberg, L., Zielinski, P., Deep anterior cerebellar stimulation reduces symptoms of secondary dystonia in patients with cerebral palsy treated due to spasticity, Clinical Neurology and Neurosurgery, 135, 62-68, 2015	Predominantly spastic CP with secondary dystonia – examines deep anterior cerebellar stimulation.
Sommerfelt, K, Markestad, T, Berg, K, Saetesdal, I, Therapeutic electrical stimulation in cerebral palsy: a randomized, controlled, crossover trial, Developmental Medicine and Child Neurology, 43, 609-13, 2001	Neuromuscular stimulation - age <12 years
Ubhi, T, Bhakta, Bb, Ives, Hl, Allgar, V, Roussounis, Sh, Randomised double blind placebo controlled trial of the effect of botulinum toxin on walking in cerebral palsy, Archives of Disease in Childhood, 83, 481-7, 2000	Not predominantly dystonic cerebral palsy. Age <16 years
Volkmann, J., Wolters, A., Kupsch, A., Muller, J., Kuhn, A. A., Schneider, G. H., Poewe, W., Hering, S., Eisner, W., Muller, J. U., Deuschl, G., Pinsker, M. O., Skogseid, I. M., Roeste, G. K., Krause, M., Tronnier, V., Schnitzler, A., Voges, J., Nikkhah, G., Vesper, J., Classen, J., Naumann, M., Benecke, R., Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial, The	Primary dystonia

Excluded studies - A.3 Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?	
Study	**Reason for Exclusion**
Lancet Neurology, 11, 1029-1038, 2012	
Walker, R. H., Danisi, F. O., Swope, D. M., Goodman, R. R., Germano, I. M., Brin, M. F., Intrathecal baclofen for dystonia: Benefits and complications during six years of experience, Movement Disorders, 15, 1242-1247, 2000	1/14 included had CP
Wloch, A., Abdallat, M., Saryyeva, A., Blahak, C., Wolf, J., Schrader, C., Runge, J., Krauss, J. K., Complications of deep brain stimulation for secondary dystonia in the early postoperative period (30-day morbidity): An experience in 49 patients, Journal of Neural Transmission, 123 (12), 1525, 2016	Abstract only. 17/49 had CP - their results are not reported separately
Wong, C, Pedersen, Sa, Kristensen, Bb, Gosvig, K, Sonne-Holm, S, The Effect of Botulinum Toxin A Injections in the Spine Muscles for Cerebral Palsy Scoliosis, Examined in a Prospective, Randomized Triple-blinded Study, Spine, 40, E1205-11, 2017	Not dystonia, age <=18 years

1 Economic studies

2 No economic evidence was identified for this review.

3

Appendix L – Research recommendations

Research recommendations for review question A3: Which treatments (pharmacological treatment (levodopa, anticholinergic drugs, and botulinum toxin injections), neurosurgical procedure (deep brain stimulation, ITB) are most effective for managing dystonia in adults with cerebral palsy where dystonia is the predominant abnormality of tone?

No research recommendation was made for this review.