COST-EFFECTIVENESS ANALYSIS

DEEP BRAIN STIMULATION IN PARKINSON'S DISEASE

WITH EARLY MOTOR COMPLICATIONS

APPENDIX

SYSTEMATIC REVIEW & DATA ANALYSES

The analysis was commissioned and financed by Medtronic International Trading Sàrl

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APPENDIX A. SYSTEMATIC REVIEWS

The following sections present detailed information on the systematic reviews of evidence that informed the economic analysis.

At all stages of each review the study selection was performed independently by two analysts. Verification at the level of abstracts and titles was carried out in such a way that all reports deemed useful by at least one of the analysts were enrolled to the next stage. In case of disagreements during the verification based on the full-text publications, the final decision on inclusion or exclusion was agreed by discussion and consensus.

Extraction of data from the studies included in the analysis was carried out by one of the analysts. Then the extraction was verified by a second analyst.

A.1. CSAI / CDLCI data

A.1.1. Search strategy

In order to identify data on effectiveness and safety of CSAI and CDLCI a systematic search was performed. Due to the fact that search was performed at the initial phase of the project, when model structure and data included in the analysis were unknown, broad inclusion criteria were defined (details in Table 4). Once the model structure was decided, selection criteria were narrowed to include only studies reporting CSAI/CDLCI effectiveness measured in terms of UPDRS scores.

Additionally, studies reporting data on safety, withdrawal and CSAI dose were selected from the studies initially included in full text analysis.

The following databases were searched for papers published from the inception of each database to 2015:

- Medline (via PubMed),
- Embase,
- The Cochrane Library.

The search was performed on 11th February 2015. Search strategies are outlined in Table 1, Table 2 and Table 3.

Table 3Table 1.
Search strategy in Medline database – CSAI / CDLCI effectiveness

Search	Search terms	Results
#1	Parkinson's disease	77 361
#2	"Parkinson Disease"[Mesh]	48 070
#3	Parkinson*	95 011
#4	parkinsonism OR (parkinsonian syndrome)	64 465
#5	paralysis agitans	57 763
#6	(#1 OR #2 OR #3 OR #4 OR #5)	96 372
#7	(apomorphine OR apomorfine)	11 324
#8	"Apomorphine"[Mesh]	8531
#9	"apomorphine hydrochloride"	95
#10	("Apo go" OR "Apo-go")	4
#11	Britaject OR Dacepton OR Apokyn OR Apokinon OR Ixense OR Spontane OR Uprima	11 339
#12	non-selective dopamine agonist	366
#13	#7 OR #8 OR #9 OR #10 OR #11 OR #12	11 586
#14	infusion	196 243
#15	continuous infusion	32 082
#16	CSI	2967
#17	subcutaneous	118 734
#18	(#14 OR #15 OR #16 OR #17)	310 377
#19	#13 AND #18	967
#20	Duodopa	478
#21	"carbidopa, levodopa drug combination"[Supplementary Concept]	446
#22	(carbidopa/levodopa) OR levocarb	157
#23	levodopa AND carbidopa	2207
#24	#20 OR #21 OR #22 OR #23	2224
#25	(infusion OR gel) OR (jejun* OR intrajejun* OR duoden* or intraduoden* OR intestinal OR intraintestinal OR enteral)	1 153 466
#26	#24 AND #25	230
#27	#19 OR #26	1161
#28	#6 AND #27	614
Search strategy executed on 11th February 2015		

Table 2.
Search strategy in Embase database – CSAI / CDLCI effectiveness

Search	Search terms	Results
#1	parkinsons AND ('disease'/exp OR disease) AND [embase]/lim	1022
#2	'parkinson disease'/exp OR 'parkinson disease' AND [embase]/lim	89 073
#3	parkinson* AND [embase]/lim	126 492
#4	'parkinsonism'/exp OR parkinsonism OR (parkinsonian AND ('syndrome'/exp OR syndrome)) AND [embase]/lim	29 576
#5	paralysis AND agitans AND [embase]/lim	105
#6	#1 OR #2 OR #3 OR #4 OR #5	126 522
#7	'apomorphine'/exp OR apomorphine OR 'apomorfine'/exp OR apomorfine AND [embase]/lim	17 499
#8	'apomorphine'/exp OR 'apomorphine' AND [embase]/lim	17 498
#9	'apomorphine hydrochloride'/exp OR 'apomorphine hydrochloride' AND [embase]/lim	16 478
#10	'apo go'/exp OR 'apo go' OR 'apo-go'/exp OR 'apo-go' AND [embase]/lim	16 470
#11	britaject OR dacepton OR 'apokyn'/exp OR apokyn OR 'apokinon'/exp OR apokinon OR 'ixense'/exp OR ixense OR spontane OR 'uprima'/exp OR uprima AND [embase]/lim	17 381
#12	'non selective' AND ('dopamine'/exp OR dopamine) AND ('agonist'/exp OR agonist) AND [embase]/lim	305
#13	#7 OR #8 OR #9 OR #10 OR #11 OR #12	18 605
#14	'infusion'/exp OR infusion AND [embase]/lim	257 682
#15	continuous AND ('infusion'/exp OR infusion) AND [embase]/lim	58 590
#16	csi AND [embase]/lim	4294
#17	'subcutaneous'/exp OR subcutaneous AND [embase]/lim	287 651
#18	#14 OR #15 OR #16 OR #17	531 563
#19	#13 AND #18	4189
#20	'duodopa'/exp OR duodopa AND [embase]/lim	4732
#21	levocarb AND [embase]/lim	6
#22	'levodopa'/exp OR levodopa AND ('carbidopa'/exp OR carbidopa) AND [embase]/lim	8167
#23	#20 OR #21 OR #22	8172
#24	'infusion'/exp OR infusion OR 'gel'/exp OR gel OR jejun* OR intrajejun* OR duoden* OR intraduoden* OR intestinal OR intraintestinal OR enteral AND [embase]/lim	879 414
#25	#23 AND #24	675
#26	#19 OR #25	4669
#27	#6 AND #26	1770
Search strategy executed on 11th February 2015		

Table 3.
Search strategy in Cochrane Library database – CSAI / CDLCI effectiveness

Search	Search terms	Results
#1	Parkinson's disease	3415
#2	MeSH descriptor: [Parkinson Disease] explode all trees	2307
#3	Parkinson*	5017
#4	parkinsonism OR (parkinsonian syndrome)	1067
#5	paralysis agitans	4
#6	(#1 OR #2 OR #3 OR #4 OR #5)	5017
#7	(apomorphine OR apomorfine)	281
#8	MeSH descriptor: [Apomorphine] explode all trees	156
#9	"apomorphine hydrochloride"	18
#10	("Apo go" OR "Apo-go")	0
#11	Britaject OR Dacepton OR Apokyn OR Apokinon OR Ixense OR Spontane OR Uprima	52
#12	non-selective dopamine agonist	11
#13	#7 OR #8 OR #9 OR #10 OR #11 OR #12	341
#14	infusion	30 308
#15	continuous infusion	7975
#16	CSI	208
#17	subcutaneous	11 779
#18	(#14 OR #15 OR #16 OR #17)	40 615
#19	#13 AND #18	84
#20	Duodopa	3
#21	levocarb	0
#22	levodopa AND carbidopa	449
#23	#20 OR #21 OR #22	449
#24	(infusion OR gel) OR (jejun* OR intrajejun* OR duoden* or intraduoden* OR intestinal OR intraintestinal OR enteral)	54 220
#25	#23 AND #24	38
#26	#19 OR #25	120
#27	#6 AND #26	70
Search strategy executed on 11th February 2015		

A.1.2. Studies selection

All studies identified within search process were initially assessed based on title and abstracts. Papers not meeting predefined inclusion criteria as indicated by title and abstracts were excluded.

In Table 4 below selection criteria defined according to PICO scheme are shown.

Table 4.
Selection criteria for clinical studies on CSAI / CDLCI effectiveness in Parkinson Disease

Criterion	Inclusion	Exclusion
Population	• Adult patients with Parkinson's disease	• Other
Intervention	• CSAI • CDLCI	• Other
Comparators	• Not relevant	–

Outcomes	• Efficacy:
	  • *UPDRS score,*
	  • *Hoehn and Yahr scale,*
	  • *'off" state time,*
	  • *Dyskinesia,*
	  • *QoL measured by PDQ-39, PDQ-8, EQ-5D,*
	• Safety, mortality.
		• Lack of interesting outcomes

Study design	• RCT, • Observational studies, • Registries, • Case series.	• Cross-over studies, if no results were presented before patients cross, • Follow-up < 1 week, • Case series or studies with < 10 patients.
Other	• Primary studies, • Publications available in full-text, • Publications in English.	• Reviews, systematic reviews, meta-analysis, • Comments, editorials, letters, • Conference abstracts (unless concern results of primary study independently identified in search).
Publication date	• Not relevant (up to date of the search - 11th February 2015)	–

Forty one studies (described in 49 publications) were included after full text analysis based on selection criteria. Additionally for 3 of finally included studies datasets on clinicaltrials.gov website for 3 studies were found and analysed. [1–6].

For the purposes of the economic analysis, additional selection was done and studies were excluded from final calculations of effectiveness due to one of the following reasons:

- no data on UPDRS or UPDRS not measured in ON-meds condition,
- insufficient data on UPDRS (only at baseline or no baseline values),
- results presented as medians,
- results presented at non-specified time points, e.g. after mean or median follow-up.

Studies were also included in final analysis if any of the following data was reported: CSAI mean daily dose, frequency of adverse events (specifically skin nodules / skin reaction for CSAI and peritonitis for CDLCI) and withdrawal rates.

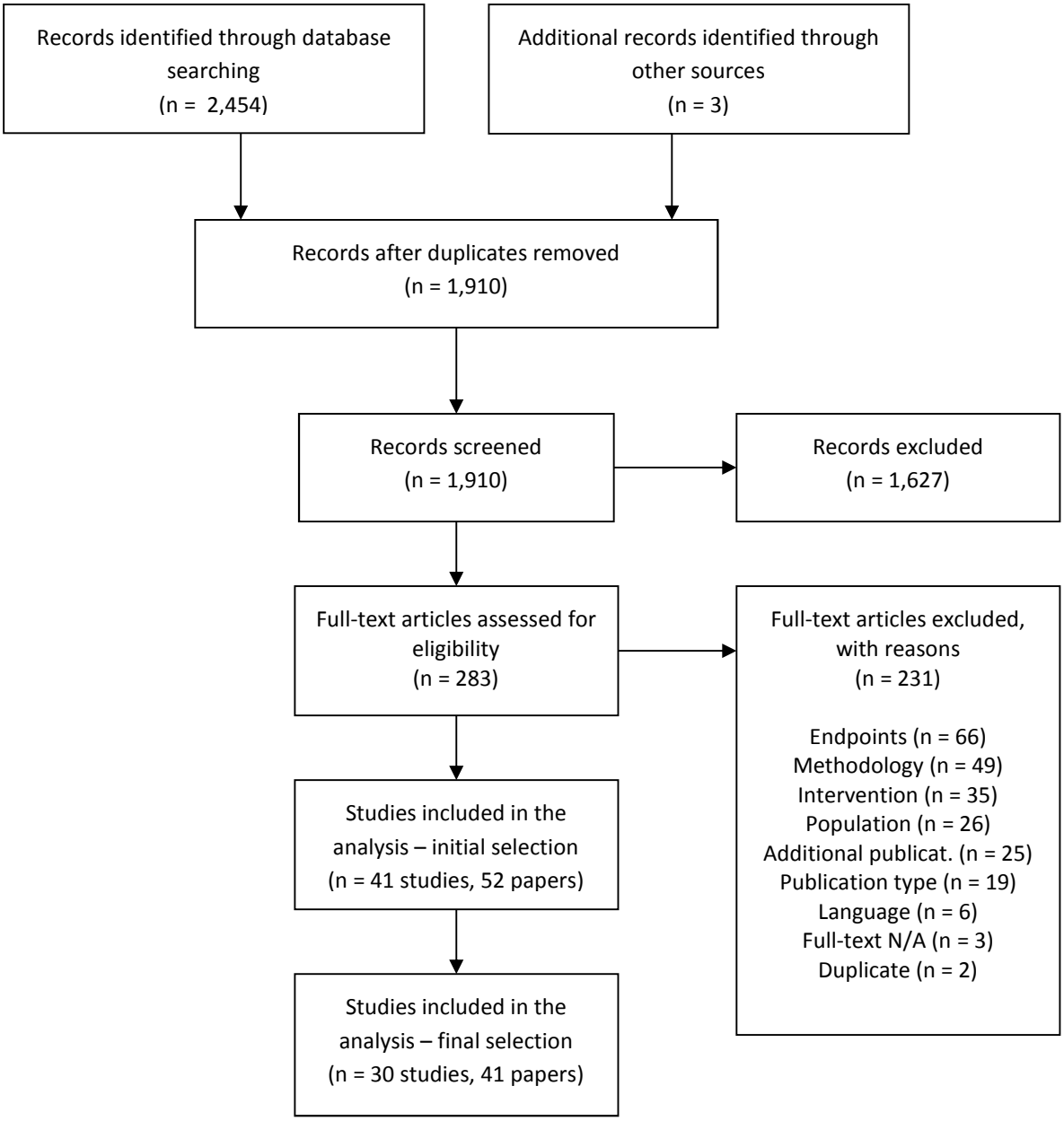
A brief summary of all 3 searches and results of studies selection is presented in the table below. The sequential phases of the review process are also illustrated in the PRISMA flow diagram (Figure 1).

Table 5.
Summary of systematic search for CSAI / CDLCI effectiveness

Search date	Database	No. of abstracts returned	Initial selection		Final no. of included studies
			No. included in full text analysis	No. of included studies	
11th February 2015	Pubmed, Embase, Cochrane	2,454	280	41 studies 49 publications 3 additional from CT	30 studies 38 publications 3 additional from CT

CT – clinicaltrials.gov; in 3 studies data both for CSAI and CDLCI

Figure 1.
Overview of studies selection: PRISMA flowchart – CSAI/CDLCI data



In Table 6 and Table 7 a brief summary of the type of data identified in all 41 initially included studies is presented. 16 studies were identified initially for CSAI, 23 for CDLCI and 2 studies reported both

CSAI and CDLCI data (Elia 2012 [7], Martinez-Martin 2014 [8]). No long term (follow-up longer than 2 years) effectiveness studies for CSAI and CDLCI meeting inclusion criteria were identified.

The list of studies included in final analysis for particular data categories together with data extracted from the studies are presented in the following sections:

- CSAI effectiveness – section A.1.3.1,
- other CSAI parameters – section A.1.3.2,
- CDLCI effectiveness – section A.1.3.3,
- other CDLCI parameters – section A.1.3.4.

Table 6.
Studies initially included in the analysis and final selection – CSAI

Study	Initial selection	Final selection		
		Effectiveness	Safety[b]	Other
Colzi 1998 [9]	off-time, dyskinesia	OUT: (no UPDRS)	OUT	-
De Gaspari 2006 / Antonini 2011 [10, 11]	UPDRS, off-time, safety	IN[a]	IN	APO dose, treatment withdrawal
Drapier 2012 [12]	UPDRS, H&Y, dyskinesia, safety	IN	IN	APO dose, treatment withdrawal
Elia 2012 [7]	UPDRS, off-time, safety	OUT (mean follow-up)	IN	-
Garcia-Ruiz 2008 [13]	UPDRS, off-time, dyskinesia, safety	OUT (mean follow-up)	IN	APO dose
Hughes 1993 / Frankel 1990 [14, 15]	off-time, safety	OUT: (no UPDRS)	IN	APO dose, treatment withdrawal
Kanovsky 2002 [16]	UPDRS, off-time, dyskinesia, safety	IN for IV OUT for III[c]	OUT	-
Katzenschlager 2005 [17]	off-time, dyskinesia, safety	OUT: (no UPDRS)	IN	APO dose, treatment withdrawal
Manson 2002 [18]	off-time, dyskinesia, safety	OUT: (no UPDRS)	OUT	APO dose, treatment withdrawal
Martinez-Martin 2011 [19]	UPDRS, Qol	IN for IV OUT for III[c]	OUT	-
Martinez-Martin 2014 [8]	UPDRS, Qol, safety		OUT	APO dose, treatment withdrawal
Morgante 2004 / di Rosa 2003 [20, 21]	off-time, safety	OUT: (no UPDRS)	IN	APO dose, treatment withdrawal
Pietz 1998 [22]	H&Y, off-time, dyskinesia, safety	OUT: (no UPDRS)	IN	-
Pinter 1998 [23]	off-time	OUT: (no UPDRS)	OUT	-
Poewe 1993 [24, 25]	off-time, safety	OUT: (no UPDRS)	IN	APO dose, treatment withdrawal
Stibe 1988 [26]	off-time, safety	OUT: (no UPDRS)	IN	APO dose
Stocchi 2001 [27]	dyskinesia, safety	OUT: (no UPDRS)	OUT	APO dose
Todorova 2013 [28]	UPDRS, Qol, safety	IN	OUT	APO dose, treatment withdrawal

a) only 1 year data; additional results after mean follow-up presented; b) included if detailed data on skin nodules occurrence reported; c) unclear whether UPDRS III was measured ON-meds or OFF-meds

Table 7.
Studies initially included in the analysis and final selection – CDLCI

Study	Available data	Inclusion in final CUA		
		Effectiveness [a]	Safety	Other
Antonini 2008 [29]	UPDRS, off-time, dyskinesia, QoI	IN for III-IV OUT for II[b]	OUT	-
Antonini 2013 [30]	UPDRS, off-time, dyskinesia, QoI, safety	IN	IN	-
Antonini 2014 (GLORIA) [31]	UPDRS, off-time, dyskinesia, QoI, safety	IN	OUT	treatment withdrawal
Caceres-Redondo 2014 [32]	UPDRS, off-time, dyskinesia, QoI, safety	IN	OUT	-
Devos 2009 [33]	UPDRS, H&Y, safety	OUT (insufficient data)	IN	-
Eggert 2008 [34]	off-time, dyskinesia, safety	OUT: (no UPDRS)	OUT	treatment withdrawal
Elia 2012 [7]	UPDRS, off-time, safety	OUT (mean follow-up)	OUT	-
Fasano 2012 [35]	UPDRS, off-time, QoI, safety	OUT (mean follow-up)	OUT	-
Fernandez 2014 [1, 4, 36, 37]	UPDRS, off-time, dyskinesia, QoI, safety	IN for I–III OUT for IV (mean follow-up)	IN	treatment withdrawal
Foltynie 2013 [38]	off-time, dyskinesia, QoI, safety	OUT: (no UPDRS)	OUT	-
Honig 2009 [39]	UPDRS, off-time, QoI	IN	OUT	-
Isacson 2008 [40]	off-time, QoI	OUT: (no UPDRS)	OUT	-
Karlsborg 2010 [41]	UPDRS, safety	IN	OUT	-
Lundqvist 2014 [42]	UPDRS, H&Y, off-time, dyskinesia, safety, QoI	OUT: (no UPDRS)	OUT	-
Martinez-Martin 2014 [8]	UPDRS, QoI, safety	IN for IV OUT for III[b]	IN	-
Meppelink 2011 [43]	UPDRS, QoI, safety	OUT (unclear measure condition)	OUT	-
Merola 2011 [44]	UPDRS, off-time, dyskinesia, safety	OUT (mean follow-up)	OUT	-
Nyholm 2008 [45]	dyskinesia, safety	OUT: (no UPDRS)	IN	treatment withdrawal

Study	Available data	Inclusion in final CUA		
		Effectiveness [a]	Safety	Other
Olanow 2014 / Slevin 2015 [2, 3, 5, 6]	UPDRS, off-time, dyskinesia, QoL, safety	IN for I–III OUT for IV (insufficient data)	OUT	treatment withdrawal
Palhagen 2012 [46]	UPDRS, QoL, safety	IN for III-IV OUT for II[b]	IN	-
Pickut 2014 [47]	UPDRS, H&Y, safety	OUT (mean follow-up)	OUT	-
Sensi 2014 [48]	UPDRS, H&Y, off-time, safety	IN	IN	-
Zibetti 2013a [49]	UPDRS	OUT (mean follow-up)	OUT	-
Zibetti 2013b [50]	UPDRS, QoL, safety	OUT (mean follow-up)	OUT	-
Zibetti 2014 [51]	UPDRS, off-time, dyskinesia, QoL, safety	OUT (mean follow-up)	IN	-

a) only data for specified time point are included; in some studies also other time point results available; b) due to unclear measurement condition – it was not reported if measured within ON med state

A.1.3. Data extraction

A.1.3.1 CSAI – effectiveness (UPDRS)

Studies included in the analysis for particular UPDRS scores are listed in Table 8. A brief description of the studies is provided in Table 9.

Table 8
CSAI studies included in final analysis – short-term effectiveness

Parameter	Short-term effectiveness			
	UPDRS I	UPDRS II	UPDRS III	UPDRS IV
Publications included	Drapier 2012	Drapier 2012	Drapier 2012, de Gaspari 2006 Todorowa 2013	Drapier 2012 Kanovsky 2002 Martinez-Martin 2011 Martinez-Martin 2014 Todorowa 2013
Total number of publications / studies	**1**	**1**	**3**	**5**

Table 9
Study characteristic – CSAI short-term effectiveness

Study	Study design	Follow-up	No of patients	Baseline patients characteristics			
				Age [mean (SD)]	Duration of PD [years (SD)]	Hoehn & Yahr (SD)	LEDD [mg (SD)]
de Gaspari 2006	**Design:** nonrandomized **Aim:** To compare clinical and neuropsychological outcome following CSAI and STN-DBS in advanced PD patients **Population:** Italy **Comparator:** STN-DBS	12 months	13	59 (13)	10 (5)	≥3	665.98 (215)
Drapier 2012	**Design:** nonrandomized, prospective **Aim:** to evaluate the efficacy and cognitive safety of CSAI **Population:** France	12 months	23	48.4 (10.5)	13.9 (8.2)	ON: 2.3 (0.9) OFF: 4.2 (1.0)	1 372.2 (325.1)
Kanovsky 2002	**Design:** nonrandomized **Aim:** To assess the effect of smaller amounts of CSAI **Population:** Czech Republic	2 years	12	64.3 (9.2)	14.4 (6.3)	4.5	1 650 (570)
Martinez-Martin 2011	**Design:** nonrandomized, multicenter, observational **Aim:** Assessing effects of CSAI therapy on non-motor symptoms and health-related quality of life **Population:** European **Comparator:** control (best conventional therapy)	Mean (SD): 12.5 (11.5) months	17	59.5 (11.7)	12.05 (4)	Median 4	1077.81 (446.26)

Study	Study design	Follow-up	No of patients	Baseline patients characteristics			
				Age [mean (SD)]	Duration of PD [years (SD)]	Hoehn & Yahr (SD)	LEDD [mg (SD)]
Martinez-Martin 2014	**Design:** nonrandomized, prospective, multicenter, observational **Aim:** Comparison of CSAI with CDLCI using validated motor, nonmotor, and quality-of-life outcome measures. **Population:** European **Comparator:** CDLCI	6 months	43	62.3 (10.6)	14 (4.4)	Median 3	1 934 (374)
Todorova 2013	**Design:** nonrandomized, prospective **Aim:** To extend the beneficial effect of 12–14 h waking day CSAI to 24 h therapy by combining with Rotigotine transdermal patch therapy and assess motor and non-motor effects **Population:** United Kingdom	2 years	15	60.3 (11.3)	15.3 (4.8)	ON: 8 patients: 3 7 patients: 4	Not reported

The data extracted from the studies finally included in the analysis (UPDRS scores and number of patients at different follow-up time points) together with percentage UPDRS changes (versus baseline) calculated for the purposes of the economic analysis are presented in Table 10.

Table 10.
CSAI effectiveness – UPDRS – data extraction

Study	UPDRS score % change vs baseline (Number of patients)			
	Baseline	6 months	1 year	2 years
UPDRS I				
Drapier 2012	2.90 (23)		2.40 -17.24% (23)	
UPDRS II (on meds)				
Drapier 2012	10.20 (23)		11.00 7.84% (23)	
UPDRS III (on meds)				
Drapier 2012	18.30 (23)		21.80 19.1% (23)	
De Gaspari 2006	19.50 (13)		19.25 -1.3% (13)	
Todorowa 2013	33.00 (20)	-		14.50 -56.1% (15)

Study	UPDRS score % change vs baseline (Number of patients)			
	Baseline	6 months	1 year	2 years
UPDRS IV				
Drapier 2012	7.70 (23)	-	6.90 -10.4% (23)	-
Kanovsky 2002	10.80 (12)	5.40 -50.0% (12)	5.30 -50.9% (12)	5.40 -50.0% (12)
Martinez-Martin 2011	10.00 (17)	-	3.53 -64.7% (17)	-
Martinez-Martin 2014	10.02 (43)	5.93 -40.8% (43)	-	-
Todorowa 2013	11.30 (20)	-	-	5.20 -54.0% (15)

Detailed information on further data analysis and final model assumptions are presented in section B.1.1.

A.1.3.2 CSAI – other parameters

Studies included in the analysis for particular data categories are listed in Table 11.

Table 11
CSAI studies included in final analysis – other parameters

Parameter	Withdrawal	Adverse effects	Dose
Publications included	Antonini 2011 / de Gaspari 2006 di Rosa 2003 / Morgante 2004 Drapier 2012 Frankel 1990 / Hughes 1993 Katzenschlager 2005 Manson 2002 Martinez-Martin 2014 Poewe 1993 Todorova 2013	Antonini 2011 / de Gaspari 2006 di Rosa 2003 / Morgante 2004 Drapier 2012 Elia 2012 Frankel 1990 / Hughes 1993 Garcia-Ruiz 2008 Katzenschlager 2005 Pietz 1998 Poewe 1993 Stibe 1988	Antonini 2011 / de Gaspari 2006 di Rosa 2003 / Morgante 2004 Drapier 2012 Frankel 1990 / Hughes 1993 Garcia-Ruiz 2008 Katzenschlager 2005 Manson 2002 Martinez-Martin 2014 Poewe 1993 Stibe 1988 Stocchi 2001 Todorova 2013
Total number of publications/studies	**12/9**	**13/10**	**15/12**

Withdrawal data

The data extracted from the studies included in the analysis is presented in Table 12. Detailed information on final model assumptions is presented in section B.4.1.

Table 12.
CSAI withdrawal – data extraction

Study	Total number of patients	Discontinuation		Follow-up [years]	Withdrawal reasons
		Number of patients	% of patients		
Antonini 2011 / de Gaspari 2006	12	6	50.0%	5.00 / 2.50 [a / b]	AEs or no effectiveness
Drapier 2012	23	0	0.0%	1.00 [a]	-
Hughes 1993 / Frankel 1990	25	6	24.0%	3.04 [b]	AEs (4), other (2)
Katzenschlager 2005	12	0	0.0%	0.50 [a]	-
Manson 2002	64	8	12.5%	2.82 [b]	AEs (3), patient's decision (2), unable to continue (3)
Martinez-Martin 2014	43	0	0.0%	0.50 [a]	-
Morgante 2004 / di Rosa 2003	12	1	8.3%	2.00 [a]	Infection
Poewe 1993	18	4	22.2%	1.72 [b]	AEs (3), no effectiveness (1)
Todorova 2013	20	5	25.0%	2.00 [a]	Skin reaction

a) total follow-up of the study; b) mean follow-up

Adverse events data

Data on skin reaction / skin nodules frequency was retrieved from the studies identified in the systematic review, as these were the most common adverse event for CSAI treatment reported in the literature. Other adverse events reported in the literature were not included in the model, as they were considered too rare (occurring in less than 5% of patients) or not influencing patient's quality of life or cost-generating.

The data extracted from the studies included in the analysis (only studies reporting frequency of skin nodules / skin reaction) is presented in Table 13. Detailed information on final model assumptions is presented in section B.3.1.

Table 13.
CSAI related adverse events – skin nodules / skin reaction – data extraction

Study	Number of patients	Patients with events	% with events	Comment
Antonini 2011 / de Gaspari 2006	12	2	17%	Based on Antonini 2011
Drapier 2012	23	23	100%	-
Elia 2012	10	5	50%	-
Garcia-Ruiz 2008	82	56	68%	In 7 patients with severe grade
Hughes 1993 / Frankel 1990	25	25	100%	Based on Frankel 1990
Katzenschlager 2005	12	9	75%	-
Morgante 2004 / di Rosa 2003	10	10	100%	Based on Morgante 2004

Study	Number of patients	Patients with events	% with events	Comment
Pietz 1998	25	25	100%	-
Poewe 1993	18	4	22%	-
Stibe 1988	11	11	100%	-

Additionally in Stocchi 1993 , Stocchi 2001 and Manson 2002 skin nodules / skin reaction occurred in almost all patients but no detailed data were presented

Dosage data

The data extracted from the studies included in the analysis is presented in Table 14. Detailed information on final model assumptions is presented in section B.5.

Table 14.
Daily doses of CSAI – data extraction

Study	Number of patients	Dose per day [mg]		Comment
		Mean	SD	
Antonini 2011 / de Gaspari 2006	12	83.40	19.20	-
Drapier 2012	23	62.60	18.80	-
Garcia-Ruiz 2008	82	72.00	21.38	-
Hughes 1993 / Frankel 1990	22	80.80	31.60[a]	data from Hughes 1993 taken; mean dose after initial stabilization
Katzenschlager 2005	8	84.70	33.13[a]	data form UK patients group
Manson 2002	45	102.50	71.80	data from monotherapy group
Martinez-Martin 2014	43	105.90	23.20	-
Morgante 2004 / di Rosa 2003	12	100.00	39.11[a]	-
Poewe 1993	14	160.00	62.58[a]	data from patients with complete follow-up
Stibe 1988	11	77.00	30.12[a]	-
Stocchi 2001	30	51.60	34.80	-
Todorova 2013	20	105.30	23.90	-

a) SD value not reported within the study; calculated based on relation of SD to mean from other studies (39.11%)

A.1.3.3 CDLCI – effectiveness

Studies included in the analysis for particular UPDRS scores are listed in Table 15. Brief description of the studies is provided in Table 16.

Table 15
CDLCI studies included in final analysis – short-term effectiveness

Parameter	Short-term effectiveness			
	UPDRS I	**UPDRS II**	**UPDRS III**	**UPDRS IV**
Publications included	Fernandez 2014 Olanov 2014 / Slevin 2015	Antonini 2013 Antonini 2014 (GLORIA) Caceres-Redondo 2014 Fernandez 2014 Olanov 2014 / Slevin 2015	Antonini 2008 Antonini 2013 Antonini 2014 (GLORIA) Caceres-Redondo 2014 Fernandez 2014 Honig 2009 Karlsborg 2010 Olanow 2014 / Slevin 2015 Palhagen 2012 Sensi 2014	Antonini 2008 Caceres-Redondo 2014 Honig 2009 Martinez-Martin 2014 Palhagen 2012 Sensi 2014
Total number of publications/studies	**3/2**	**6/5**	**11/10**	**6**

Table 16
Study characteristic – CDLCI short-term effectiveness

Study	Study design	Follow-up	No of patients	Baseline patients characteristics			
				Age [mean (SD)]	**Duration of PD [years (SD)]**	**Hoehn & Yahr (SD)**	**LEDD [mg (SD)]**
Antonini 2008	**Design:** nonrandomized, prospective, multicenter **Aim:** To assess the effectiveness of CDLCI on quality of life as well as motor features in patients with advanced PD **Population:** Italy	2 years	22	Not reported	Not reported	≥3	Not reported
Antonini 2013	**Design:** nonrandomized, retrospective, multicenter, cohort **Aim:** Assessment of long-term safety and outcome of chronic treatment with CDLCI **Population:** European	Up to 2 years	98	68.9 (14.6)	14.9 (6.6)	OFF: 3.9 (1.0)	973 (636)
Antonini 2014 (GLORIA)	**Design:** nonrandomized, observarional, multicenter **Aim:** To record long-term effectiveness of advanced PD patients undergoing CDLCI infusion **Population:** 18 countries (17 european and Australia)	1 year	172	66.5 (9.3)	12.6 (6.6)	2.8 (0.8)	Not reported
Caceres-Redondo 2014	**Design:** nonrandomized, single center **Aim:** investigate the motor and cognitive outcome of CDLCI treatment in advanced PD **Population:** Spain	2 years	16	64.5 (9.0)	14.1 (3.9)	ON: 2.4 (0.5) OFF: 3.7 (0.8)	1 306.1 (337.6)

Study	Study design	Follow-up	No of patients	Baseline patients characteristics			
				Age [mean (SD)]	Duration of PD [years (SD)]	Hoehn & Yahr (SD)	LEDD [mg (SD)]
Fernandez 2014	**Design:** nonrandomized, prospective, multicenter **Aim:** To provide long-term safety and efficacy data for advanced PD patients **Population:** 16 countries	54 weeks	354	64.1 (9.1)	12.5 (5.5)	Not reported	1 082.9 (582.1)
Honig 2009	**Design:** nonrandomized, prospective, observational, multicenter **Aim:** Assessing effects of CDLCI on nonmotor symptoms of advanced PD and on the relationship with motor changes and health related quality of life **Population:** United Kingdom, Germany, Italy	6 months	22	58.6 (9.1)	15.3 (5.9)	OFF: 3.75 (0.84)	Not reported
Karlsborg 2010	**Design:** nonrandomized **Aim:** To report the effect of Duodopa treatment on PD patients' "on" state as measured by the UPDRS III and their motor fluctuations and dyskinesias. **Population:** Denmark	Mean for 12 patients: 16.3 (15.7)	14	64.9 (13.5)	16.2 (7.4)	3.3 (0.7)	1316.5 (845.7)
Martinez-Martin 2014	**Design:** nonrandomized, prospective, multicenter, observational **Aim:** Comparison of CSAI with CDLCI using validate motor, nonmotor, and quality-of-life outcome measures. **Population:** European **Comparator:** CSAI	6 months	44	62.7 (9.1)	16.1 (6.7)	Median: 4	2 017 (857.2)
Olanow 2014	**Design:** RCT, prospective, multicentre, **Aim:** To assess safety and efficacy of CDLCI in patients with advanced PD **Population:** Germany, New Zealand, USA **Comparator:** placebo	12 weeks	37	63.7 (9.5)	10.0 (4.6)	Not reported	1005.4 (373.6)
Slevin 2015	**Design:** open-label extension of RCT **Aim:** To examine long-term safety, efficacy and quality of life of CDLCI **Population:** Germany, New Zealand, USA **Comparator:** placebo	1 year	33	63.6 (9.0)	10.07 (4.84)	Not reported	Not reported
Palhagen 2012	**Design:** nonrandomized, prospective **Aim:** To investigate clinical and health-related quality of life effects of CDLCI **Population:** Norway, Sweden	12 months	27	64.6 (6.4)	12.6	Not reported	Not reported

Study	Study design	Follow-up	No of patients	Baseline patients characteristics			
				Age [mean (SD)]	Duration of PD [years (SD)]	Hoehn & Yahr (SD)	LEDD [mg (SD)]
Sensi 2014	**Design:** nonrandomized, prospective, single center **Aim:** To detect any predictive factor to identify the best candidates for CDLCI therapy **Population:** Italy	32.47 (9.47) months	17	67.6 (6.1)	15.47 (4.04)	3.17 (0.8)	1158.9 (334.5)

The data extracted from the studies included in the analysis (UPDRS scores and number of patients at different follow-up time points) together with percentage UPDRS changes (versus baseline) calculated for the purposes of the economic analysis are presented in Table 17.

Table 17.
CDLCI effectiveness – UPDRS – data extraction

Study	UPDRS score / % change vs baseline (Number of patients)					
	Baseline	4 weeks	12 weeks	6 months	1 year	2 years
UPDRS I						
Fernandez 2014	2.20 (288)	-	-	-	2.20 / 0.00% (272[a])	-
Olanov 2014 / Slevin 2015[b]	1.80 (36)	-	1.60 / -11.1% (36)	-	2.10 / 16.7% (33)	-
Olanov 2014 / Slevin 2015[c]	1.80 (33)	-	-	-	2.50 / 38.9% (26)	-
UPDRS II (on meds)						
Antonini 2013	14.78 (73)	-	-	10.64 / -28.1% (53)	11.83 / -20.0% (43)	13.95 / -5.7% (33)
Antonini 2014 (GLORIA)	16.50 (172)	-	-	14.40 / 12.7% (69)	13.40 / -18.8% (56)	-
Caceres-Redondo 2014	14.50 (16)	-	-	-	-	16.50 / 13.8% (16)
Fernandez 2014	17.40 (293)	11.80 / -32.2% (286)	12.00 / -31.0% (279)	12.10 / -30.5% (269)	13.20 / -24.1% (251)	-
Olanov 2014 / Slevin 2015[b]	11.60 (36)	-	9.80 / -15.5% (35)	-	12.10 / 4.3% (33)	-
Olanov 2014 / Slevin 2015[c]	11.80 (33)	-	-	-	10.80 / -8.5% (26)	-

Study	UPDRS score / % change vs baseline (Number of patients)					
	Baseline	4 weeks	12 weeks	6 months	1 year	2 years
UPDRS III (on meds)						
Antonini 2008	24.60 (22)	-	-	-	23.80 / -3.3% (22)	24.80 / 0.8% (22)
Antonini 2013	25.34 (73)	-	-	22.58 / -10.9% (55)	23.33 / -7.9% (47)	27.05 / 6.7% (29)
Antonini 2014 (GLORIA)	26.50 (172)	-	-	23.50 / -11.3% (87)	23.20 / -12.5% (74)	-
Caceres-Redondo 2014	27.20 (16)	-	-	-	-	29.50 / 8.5% (16)
Fernandez 2014	28.80 (291)	19.00 / -34.0% (286)	20.00 / -30.6% (279)	19.70 / -31.6% (269)	20.80 / -27.8% (251)	-
Honig 2009	19.10 (22)	-	-	11.60 / -39.3% (22)	-	-
Karlsborg 2010	36.80 (12)	20.40 / -44.6% (12)	-	-	-	-
Olanow 2014 / Slevin 2015[b]	18.10 (36)	-	16.60 / -8.3% (35)	-	19.60 / 8.3% (33)	-
Olanow 2014 / Slevin 2015[c]	22.50 (33)	-	-	-	22.00 / -2.2% (25)	-
Palhagen 2012	24.40 (27)	-	-	-	21.50 / -11.9% (25)	-
Sensi 2014	35.50 (17)	-	-	33.40 / -5.9% (17)	-	-
UPDRS IV						
Antonini 2008	8.40 (22)	-	-	-	6.40 / -23.8% (22)	6.60 / -21.4% (22)
Caceres-Redondo 2014	8.70 (16)	-	-	-	-	6.70 / -23.0% (16)
Honig 2009	10.50 (22)	-	-	4.50 / -57.1% (22)	-	-
Martinez-Martin 2014	9.93 (44)	-	-	4.36 / -56.1% (44)	-	-
Palhagen 2012	9.40 (27)	-	-	-	5.70 / -39.4% (25)	-

Study	UPDRS score / % change vs baseline (Number of patients)					
	Baseline	4 weeks	12 weeks	6 months	1 year	2 years
Sensi 2014	8.40 (17)	-	-	5.60 / -33.3% (17)	-	-

a) number of patients not reported, assumed the same as number of patients that completed 1-year follow-up;
b) patients randomized to CDLCI at baseline; c) patients randomized to BMT at baseline who started CDLCI after 12 weeks

Detailed information on further data analysis and final model assumptions are presented in section B.1.2.

A.1.3.4 CDLCI – other parameters

Studies included in the analysis for particular data categories are listed in Table 18.

Table 18
CDLCI studies included in final analysis – other parameters

Parameter	Withdrawal	Adverse effects
Publications included	Antonini 2014 (GLORIA) Eggert 2008 Fernandez 2014 Nyholm 2008 Palhagen 2012 Slevin 2005	Antonini 2013d Devos 2009 Fernandez 2014 Martinez-Martin 2014 Palhagan 2012 Sensi 2014 Zibetti 2014
Total number of publications	6	7

Withdrawal data

The data extracted from the studies included in the analysis is presented in Table 19. Detailed information on final model assumptions is presented in section B.4.2.

Table 19.
CDLCI withdrawal – data extraction

Study	Total number of patients	Discontinuation		Comment
		Number of patients	% of patients	
Test phase / initial treatment period				
Antonini 2014 (GLORIA)	172	8	8.5%	**Test phase:** run-in period – CDLCI infusion via nasoduodenal tube **Discontinuation reason:** not reported in details
Fernandez 2014	354	22[a]	6.2%	**Test phase:** nasojejunal (NJ) titration period (2-14 days) and a PEG-J titration period (2-14 days) **Discontinuation reason:** withdrew consent (12), AEs (5), lack of efficacy (5)

Study	Total number of patients	Discontinuation		Comment
		Number of patients	% of patients	
Nyholm 2008	58	7	12.1%	**Test phase:** nasodoudenal test period for an average 12 days (range: 3-30) **Discontinuation reason:** not reported in details
Palhagen 2012	37	10	27.0%	**Test phase:** initiation nasoduodenal CDLCI + period before permanent CDLCI implantation (3 months) **Discontinuation reason:** withdrew consent (3), AEs (2), lack of efficacy (5)
1st year of treatment				
Eggert 2008	13	4	30.8%	**Discontinuation reason:** patient's refusing (1), AEs (1), mechanical and physical problems (2)
Fernandez 2014	324	37[b]	16.0%	**Discontinuation reason:** withdrew consent (13), AEs (22), lack of efficacy (2)
Slevin 2005	29	5	17.2%	**Discontinuation reason:** withdrew consent (13), AEs (22), lack of efficacy (2)
Subsequent years				
Nyholm 2012	135	31	23.0%[c]	**Discontinuation reason:** AEs or lack of effectiveness **Time period:** mean follow-up 4.2 years; restricted mean treatment time estimated with Kaplan–Meier methodology (censoring at the end of the study or death): 7.79 years

a) additional 8 patients withdrew due to administrative reason or protocol violation. According to methodology not included in calculation
b) additional 15 patients withdrew due to administrative reason or protocol violation. According to methodology not included in calculation
c) cumulative discontinuation rate for the whole follow-up period

Adverse events data

Data on frequency of peritonitis was retrieved from the systematic review, presented in Table 20. Detailed information on final model assumptions is presented in section B.3.2.

Table 20.
CDLCI related adverse events – peritonitis – data extraction

Study	Number of patients	Peritonitis	
		Number of events	Probability of event
Antonini 2013d	98	4	4.08%
Devos 2009	91	4	4.40%
Fernandez 2014	324	9	2.78%
Martinez-Martin 2014	44	1	2.27%
Palhagan 2012	37	1	2.70%
Sensi 2014	28	2	7.14%
Zibetti 2014	59	1	1.69%

A.2. Long-term DBS effectiveness

A.2.1. Search strategy

In order to identify data on long-term effectiveness of DBS a systematic literature search was performed. Due to the fact that search was performed at the initial phase of the project, when model structure and data included in the analysis were unknown, broad inclusion criteria were defined (details in Table 24). Once the model structure was decided, selection criteria were narrowed to include only studies reporting long-term DBS effectiveness measured in terms of UPDRS scores.

The following databases were searched for papers published from the inception of each database to 2015:

- Medline (via PubMed),
- Embase,
- The Cochrane Library.

The search was performed on 10th March 2015. Search strategies are outlined in Table 21, Table 22 and Table 23.

Table 21.
Search strategy in Medline database – DBS effectiveness

Search	Search terms	Results
1	Parkinson's disease	77779
2	"Parkinson Disease"[Mesh]	48251
3	Parkinson*	95489
4	(parkinsonism OR (parkinsonian syndrome))	64722
5	paralysis agitans	58046
6	#1 OR #2 OR #3 OR #4 OR #5	96856
7	"Deep Brain Stimulation"[Mesh]	4871
8	DBS	5568
9	globus pallidus interna stimulation	154
10	subthalamic nucleus stimulation	3206
11	#7 OR #8 OR #9 OR #10	8956
12	#6 AND #11	4025
13	((((Control or prospective or comparative* OR cohort* OR "cohort studies" OR (cohort and (study OR studies)) OR (cohort analy*) OR retrospectiv* OR observational OR (observational AND (study OR studies)) OR "cross-sectional" OR "cross sectional" OR "cross sectional" OR "cross-sectional studies" OR "case control studies" OR "Case control" OR ("follow up" and (study OR studies)) OR longitudinal Or retrospective OR (clinical AND (study OR trial)) OR crossover OR "cross-over" OR population-based OR survey OR register OR registry OR "case series"))))	7601004
14	((((((("randomized controlled trial") OR (random*) OR (RCT) OR (((singl* OR doubl* OR trebl* OR tripl*) AND (blind* OR mask*)) OR (single blind) OR (double blind) OR (triple blind) OR (placebo) OR (placebo-controlled) OR (blinding) OR (controlled clinical trial) OR (random* AND controlled AND study*) OR (random* AND controlled AND trial*) OR ((random OR randomly) AND (allocation OR allocate*))))))))	1100157

Search	Search terms	Results
15	#13 OR #14	7836229
16	#12 AND #15	2190
	Search strategy executed on 10th March 2015	

Table 22.
Search strategy in Embase database – DBS effectiveness

Search	Search terms	Results
1	parkinsons AND ('disease' OR 'disease'/exp OR disease) AND [embase]/lim	**1,062**
2	'parkinson disease'/exp OR 'parkinson disease' AND [embase]/lim	89,484
3	parkinson* AND [embase]/lim	**127,144**
4	'parkinsonism' OR 'parkinsonism'/exp OR parkinsonism OR (parkinsonian AND ('syndrome' OR 'syndrome'/exp OR syndrome)) AND [embase]/lim	29,705
5	'paralysis'/exp OR paralysis AND agitans AND [embase]/lim	105
6	#1 OR #2 OR #3 OR #4 OR #5	127,174
7	dbs AND [embase]/lim	8,692
8	'deep brain stimulation'/exp AND [embase]/lim	27,513
9	globus AND pallidus AND interna AND ('stimulation'/exp OR stimulation)	313
10	subthalamic AND nucleus AND ('stimulation'/exp OR stimulation)	5,018
11	#7 OR #8 OR #9 OR #10	31,357
12	#6 AND #11	8,227
13	control OR prospective OR comparative* OR cohort* OR 'cohort studies' OR (cohort AND (study OR studies)) OR (cohort AND analy*) OR retrospectiv* OR observational OR (observational AND (study OR studies)) OR 'cross-sectional' OR 'cross sectional' OR 'cross-sectional studies' OR 'case control studies' OR 'case control' OR ('follow up' AND (study OR studies)) OR longitudinal OR retrospective OR (clinical AND (study OR trial)) OR crossover OR 'cross-over' OR 'population based' OR survey OR register OR registry OR 'case series'	9,546,035
14	'randomized controlled trial' OR random* OR rct OR (singl* OR doubl* OR trebl* OR tripl* AND (blind* OR mask*)) OR (single AND blind) OR (double AND blind) OR (triple AND blind) OR placebo OR 'placebo controlled' OR blinding OR (controlled AND clinical AND trial) OR (random* AND controlled AND study*) OR (random* AND controlled AND trial*) OR (random OR randomly AND (allocation OR allocate*))	1,482,813
15	#13 OR #14	9,810,669
16	#12 AND #15	**4,652**
	Search strategy executed on 10th March 2015	

Table 23.
Search strategy in Cochrane Library database – DBS effectiveness

Search	Search terms	Results
1	Parkinson's disease	3482
2	MeSH descriptor: [Parkinson Disease] explode all trees	2314
3	Parkinson*	5098
4	parkinsonism or (parkinsonian syndrome)	1084

Search	Search terms	Results
5	paralysis agitans	4
6	#2 or #3 or #4 or #5	5098
7	MeSH descriptor: [Deep Brain Stimulation] explode all trees	199
8	DBS	286
9	globus pallidus interna stimulation	17
10	subthalamic nucleus stimulation	190
11	#7 or #8 or #9 or #10	435
12	#7 and #11	247
Search strategy executed on 10th March 2015		

A.2.2. Study selection

All studies identified in the search were initially assessed based on title and abstracts applying predefined selection criteria listed below (Table 24). In a second step, publications initially included based on title and abstract screening, were assessed based on the full article. Papers not meeting the inclusion criteria were excluded from further evaluation.

In the table below selection criteria defined according to PICO scheme are shown.

Table 24.
Selection criteria for clinical studies on DBS effectiveness in Parkinson Disease

Criterion	Inclusion	Exclusion
Population	• Adult patients with Parkinson's disease	• Other
Intervention	• Deep brain stimulation	• Other
Comparators	• Not relevant - any comparator	–

Outcomes	• Efficacy:
	  • *UPDRS score,*
	  • *Hoehn and Yahr scale,*
	  • *'off" state time,*
	  • *Dyskinesia,*
	  • *LEDD,*
	  • *QoL measured by PDQ-39, PDQ-8, EQ-5D,*
	• Safety, mortality.
		• Lack of interesting outcomes

Study design	• RCT, • Observational studies, • Registries, • Case series.	• Cross-over studies, if no results were presented before patients cross, • Case series or studies with < 20 patients.

Criterion	Inclusion	Exclusion
Other	• Primary studies, • Publications available in full-text, • Publications in English.	• Reviews, systematic reviews, meta-analysis, • Comments, editorials, letters, • Conference abstracts (unless concern results of primary study independently identified in search), • Data not allowing to calculate change per given time period.
Publication date	• Not relevant (up to date of the search - 10th March 2015)	–

For the purposes of economic analysis, additional selection criteria were taken into account, and only studies meeting the following criteria were included:

- Studies reporting UPDRS measured ON-meds,
- Studies with results presented as mean (not median),
- Studies reporting UPDRS scores at least at two follow-up time-points with first of them at least 2 year after treatment initiation.

A brief summary of all 3 searches and results of studies selection is presented below (Table 25, Table 26). The sequential phases of the review process are also illustrated in the flow diagram (Figure 2).

The list of studies included in final analysis together with data extracted from the studies are presented in section A.2.3.

Table 25.
Summary of systematic search for DBS effectiveness studies

Search date	Database	No. of abstracts returned	Initial selection		Final no. of included studies
			No. included in full text analysis	No. of included studies	
10th March 2015	Pubmed, Embase, Cochrane	7,089	751	190 papers (Table 26)	19 papers (Table 27)

Table 26.
Studies initially included in the analysis and final selection – long-term DBS effectiveness

Study	Initial selection	Final selection	Data included in analysis			
			UPDRS I	UPDRS II	UPDRS III	UPDRS IV
Abboud 2015 [52]	QoI	OUT (no UPDRS data)	-	-	-	-
Accolla 2007 [53]	UPDRS, H&Y, off/dysk, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Aviles-Olmos 2014 [54]	UPDRS, off/dysk, LEDD, QoI, safety	IN	-	✓	✓	-
Aybek 2007 [55]	UPDRS, LEDD	IN (with Wider 2008)	-	-	✓	-

Study	Initial selection	Final selection	Data included in analysis			
			UPDRS I	UPDRS II	UPDRS III	UPDRS IV
Baba 2012 [56]	UPDRS, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Baizabal Carvallo 2012 [57]	Mortality	OUT (no UPDRS data)	-	-	–	-
Bang 2014 [58]	LEDD, safety	OUT (no UPDRS data)	-	-	-	-
Bannier 2009 [59]	UPDRS, H&Y, off/dysk, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Barichella 2003 [60]	UPDRS, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Boviatsis 2010 [61]	Safety	OUT (no UPDRS data)	-	-	–	-
Burdick 2010 [62]	Safety	OUT (no UPDRS data)	-	-	–	-
Capecci 2005 [63]	UPDRS, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Castelli 2010 [64]	UPDRS, LEDD,	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Castrioto 2013 [65]	UPDRS, off/dysk, LEDD	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Castrioto 2015 [66]	UPDRS, LEDD,	OUT (UPDRS III only baseline data)	-	-	-	-
Chandran 2014 [67]	UPDRS, H&Y, off/dysk, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Chiou 2015 [68]	UPDRS, LEDD, safety	OUT (no UPDRS data in two appropriate time points or only baseline values)	-	-	-	-
Cilia 2007 [69]	UPDRS, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Cilia 2009 [70]	UPDRS, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Cohen 2007 [71]	LEDD	OUT (no UPDRS data)	-	-	-	-
Cury 2014 [72]	UPDRS, H&Y	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Daniele 2003 [73]	UPDRS, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Daniels 2011 [74]	UPDRS, off/dysk, LEDD, Qol	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Davis 2006 [75]	UPDRS	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Deep-brain stimulation ...2001 [76]	UPDRS, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
DeLong 2014 [77]	Safety	OUT (no UPDRS data)	-	-	–	-

Study	Initial selection	Final selection	Data included in analysis			
			UPDRS I	UPDRS II	UPDRS III	UPDRS IV
Derost 2007 [78]	UPDRS, H&Y, off/dysk, LEDD, Qol, safety	OUT (no UPDRS data in two appropriate time points or data unclear)	-	-	-	-
Derrey 2008 [79]	UPDRS, H&Y, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Derrey 2010 [80]	UPDRS, off/dysk, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Deuschl 2006 [81]	UPDRS, LEDD, Qol, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Doshi 2003 [82]	H&Y, safety	OUT (no UPDRS data)	-	-	-	-
Drapier 2005 [83]	UPDRS, Qol, safety	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Erola 2005 [84]	Qol	OUT (no UPDRS data)	-	-	-	-
Erola 2006 [85]	UPDRS, H&Y, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Esselink 2004 [86]	safety	OUT (no UPDRS data)	-	-	-	-
Esselink 2009 [87]	UPDRS, safety	OUT (only medians)	-	-	-	-
Eusebio 2013 [88]	UPDRS, H&Y, off/dysk, LEDD	OUT (no UPDRS data in two appropriate time points or only baseline UPDRS value)	-	-	-	-
Evidente 2011 [89]	UPDRS, LEDD	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Falowski 2012 [90]	Safety	OUT (no UPDRS data)	-	-	–	-
Fasano 2010 [91]	UPDRS, LEDD, safety	IN	-	-	✓	-
Fenoy 2014 [92]	Safety	OUT (no UPDRS data)	-	-	–	-
Ferraye 2008 [93]	UPDRS, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Ferraye 2013 [94]	UPDRS, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Figueiras-Mendez 2002 [95]	UPDRS, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Fluchere 2014 [96]	UPDRS, H&Y, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Follett 2010 [97]	UPDRS, LEDD, Qol, safety	OUT (the same group of patients in Weaver 2012)	-	-	-	-
Ford 2004 [98]	UPDRS, H&Y, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Foubert-Samier 2012 [99]	UPDRS, LEDD	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-

Study	Initial selection	Final selection	Data included in analysis			
			UPDRS I	UPDRS II	UPDRS III	UPDRS IV
Fraix 2006 [100]	UPDRS, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Funkiewiez 2006 [101]	UPDRS, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Gan 2007 [102]	UPDRS, safety	IN (with Gervais-Bernard 2009)	✓	✓	✓	✓
George 2012 [103]	H&Y, LEDD	OUT (no UPDRS data)	-	-	-	-
Gervais-Bernard 2009 [104]	UPDRS, LEDD, safety	IN (with Gan 2007)	✓	✓	✓	✓
Gomez-Esteban 2008 [105]	UPDRS, QoI	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Guehl 2006 [106]	UPDRS, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Guo 2013 [107]	UPDRS	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Hamasaki 2010 [108]	UPDRS, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Hamel 2003 [109]	UPDRS	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Hariz 2008 [110]	Safety	OUT (no UPDRS data)	-	-	–	-
Harries 2012 [111]	UPDRS, off/dysk, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Herzog 2003 [112]	UPDRS, H&Y, off/dysk, safety	OUT (no UPDRS data in two appropriate time points or baseline data only)	-	-	-	-
Herzog 2009 [113]	UPDRS	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Houeto 2000 [114]	UPDRS, H&Y, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Houeto 2006 [115]	UPDRS, LEDD, QoI, safety	OUT (no UPDRS data in two appropriate time points or only baseline data)	-	-	-	-
Hung 2013 [116]	UPDRS, H&Y, LEDD, safety	IN (UPDRS I, IV) OUT (II, III no on med / on stim data)	-	-	-	-
Jaggi 2004 [117]	UPDRS, H&Y, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Janssen 2014 [118]	UPDRS, LEDD	IN	✓	✓	✓	✓
Jiang 2013 [119]	UPDRS, LEDD	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Kalteis 2006 [120]	UPDRS, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-

Study	Initial selection	Final selection	Data included in analysis			
			UPDRS I	UPDRS II	UPDRS III	UPDRS IV
Kenney 2007 [121]	Safety	OUT (no UPDRS data)	-	-	–	-
Kim 2012 [122]	UPDRS, H&Y, LEDD,	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Kim 2013 [123]	UPDRS, H&Y, LEDD	IN	✓	✓	✓	✓
Kim 2015 [124]	UPDRS, H&Y, LEDD, safety	OUT (data not clear, UPDRS values outside scale)	-	-	-	-
Kishore 2010 [125]	UPDRS, H&Y, off/dysk, LEDD, safety	IN	✓	✓	✓	–
Kleiner-Fisman 2003 [126]	UPDRS, LEDD, safety	OUT (median values)	-	-	-	-
Koike 2008 [127]	UPDRS, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Krack 2003 [128]	UPDRS, off/dysk, LEDD, safety	IN	-	✓	✓	-
Krause 2004 [129]	UPDRS, H&Y, off/dysk, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Kumar 2000 [130]	UPDRS, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Lagrange 2002 [131]	UPDRS, off/dysk, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Langner-Lemercier 2015 [132]	UPDRS, H&Y, LEDD, QoI	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Lee 2008 [133]	UPDRS, H&Y, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Lefaucheur 2008 [134]	UPDRS, H&Y, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Lewis 2014 [135]	UPDRS, LEDD, QoI, safety	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Lewis 2015 [136]	UPDRS, LEDD, QoI, safety	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Lhommee 2012 [137]	UPDRS, off/dysk, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Li 2013 [138]	UPDRS, LEDD, safety	IN	-	✓	-	-
Liang 2006 [139]	UPDRS, off/dysk, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Liang 2012 [140]	UPDRS, H&Y, off/dysk, safety	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Lilleeng 2014 [141]	Safety, mortality	OUT (no UPDRS data)	-	-	–	-

Study	Initial selection	Final selection	Data included in analysis			
			UPDRS I	UPDRS II	UPDRS III	UPDRS IV
Limousin 1998 [142]	UPDRS, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Liu 2013 [143]	UPDRS, LEDD, off/dysk.	OUT (excluded by clinicians)	-	-	-	-
Locke 2011 [144]	UPDRS, H&Y	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Lokkegaard 2007 [145]	LEDD	OUT (no UPDRS data)	-	-	-	-
Lyons 2004 [146]	Safety	OUT (no UPDRS data)	-	-	–	-
Lyons 2006 [147]	UPDRS, off/dysk, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Merola 2012 [148]	UPDRS, LEDD,	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Merola 2014 [149]	UPDRS, H&Y, LEDD	IN (UPDRS IV) OUT (UPDRS II, III not clear)	-	-	-	-
Minguez-Castellanos 2005 [150]	UPDRS, H&Y, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Monteiro 2014 [151]	UPDRS, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Montel 2009 [152]	UPDRS, H&Y, LEDD, Qol	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Nazzaro 2011 [153]	UPDRS, LEDD, Qol, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Ngoga 2014 [154]	Mortality	OUT (no UPDRS data)	-	-	–	-
Nilsson 2005 [155]	LEDD	OUT (no UPDRS data)	-	-	-	-
Nunta-aree 2010 [156]	UPDRS, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points or unclear results)	-	-	-	-
Odekerken 2013 [157]	UPDRS, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Ogura 2004 [158]	H&Y, off/dysk	OUT (no UPDRS data)	-	-	-	-
Okun 2012 [159]	UPDRS, H&Y, off/dysk, LEDD, Qol, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Okun 2014 [160]	UPDRS, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Ondo 2006 [161]	UPDRS, LEDD, safety	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Ory-Magne 2007 [162]	UPDRS, off/dysk, LEDD, Qol, safety	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-

Study	Initial selection	Final selection	Data included in analysis			
			UPDRS I	UPDRS II	UPDRS III	UPDRS IV
Ostergaard 2002 [163]	UPDRS, H&Y, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Ostergaard 2006 [164]	UPDRS, H&Y, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Otaka 2010 [165]	UPDRS, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Oyama 2012 [166]	UPDRS, off/dysk, LEDD	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Paek 2008 [167]	UPDRS, H&Y, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Paek 2011 [167]	UPDRS, H&Y, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Paek 2011 [168]	UPDRS, H&Y, off/dysk, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Paek 2013 [169]	UPDRS, H&Y, off/dysk, LEDD, safety	IN	-	-	✓	-
Paluzzi 2006 [170]	Safety	OUT (no UPDRS data)	-	-	–	-
Patel 2015 [171]	Safety	OUT (no UPDRS data)	-	-	–	-
Pellaprat 2014 [172]	UPDRS, LEDD, Qol, safety	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Perriol 2006 [173]	UPDRS, H&Y, LEDD	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Piboolnurak 2007 [174]	UPDRS, off/dysk, LEDD, safety	IN	-	✓	✓	-
Portman 2006 [175]	UPDRS, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Price 2011 [176]	UPDRS	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Reese 2012 [177]	UPDRS, H&Y	OUT (no on med / on stim data)	-	-	-	-
Rizzone 2014 [178]	UPDRS, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Rocha 2014 [179]	Mortality	OUT (no UPDRS data)	-	-	–	-
Rodriguez-Oroz 2005 [180]	UPDRS, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-

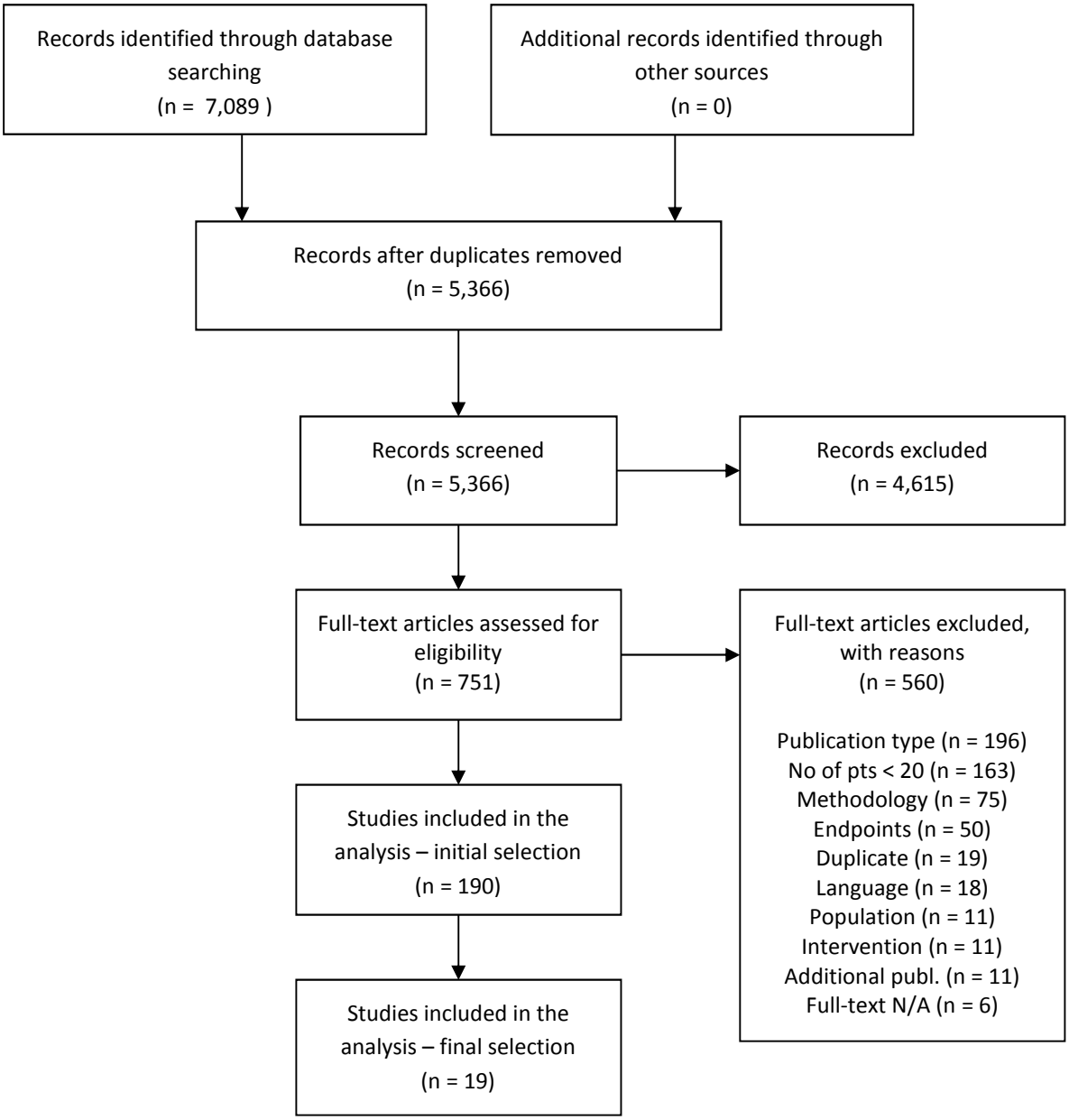
Study	Initial selection	Final selection	Data included in analysis			
			UPDRS I	UPDRS II	UPDRS III	UPDRS IV
Romito 2002 [181]	UPDRS, H&Y, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Romito 2003 [182]	UPDRS, H&Y, off/dysk, LEDD, safety	OUT (unclear measurement condition)	-	-	-	-
Romito 2009 [183]	UPDRS, off/dysk, LEDD, safety	IN (only UPDRS II) OUT (UPDRS III no on med / on stim data)	-	✓	-	-
Schlaier 2014 [184]	UPDRS, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Schupbach 2005 [185]	UPDRS, off/dysk, LEDD, safety	IN	✓	✓	✓	✓
Schupbach 2007 [186]	UPDRS, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Seijo 2007 [187]	Safety	OUT (no UPDRS data)	-	-	-	-
Seijo 2014 [188]	Safety	OUT (no UPDRS data)	-	-	-	-
Simonin 2009 [189]	UPDRS, off/dysk	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Smeding 2006 [190]	UPDRS, H&Y, safety	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Smeding 2011 [191]	UPDRS, H&Y, safety	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Soulas 2011 [192]	UPDRS, Qol, safety	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Soulas 2012 [193]	UPDRS, LEDD, Qol,	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Sung 2013 [194]	UPDRS	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Tagliati 2010 [195]	UPDRS, LEDD, safety	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Tai 2010 [196]	UPDRS, H&Y, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Tanei 2009 [197]	UPDRS, H&Y, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Tang 2015 [198]	UPDRS, safety	OUT (no UPDRS data in two appropriate time points or only baseline UPDRS value)	-	-	-	-
Tavella 2002 [199]	UPDRS, LEDD, safety	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Temel 2007 [200]	UPDRS, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-

Study	Initial selection	Final selection	Data included in analysis			
			UPDRS I	UPDRS II	UPDRS III	UPDRS IV
Tir 2007 [201]	UPDRS, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Toft 2011 [202]	UPDRS, LEDD, safety	IN	-	-	✓	-
Troche 2014 [203]	UPDRS, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Troster 2003 [204]	UPDRS, LEDD, QoI	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Tsai 2009 [205]	UPDRS, H&Y, LEDD, safety	OUT (no on med / on stim data or unclear data)	-	-	-	-
Tsai 2012 [206]	UPDRS, H&Y, LEDD, safety	OUT only baseline data or unclear measurement condition)	-	-	-	-
Tykocki 2013 [207]	UPDRS, LEDD, QoI	OUT (UPDRS III only baseline)	-	-	-	-
Tykocki 2013 [208]	UPDRS, LEDD, QoI	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Umemura 2011 [209]	Safety	OUT (no UPDRS data)	-	-	–	-
Vercruysse 2014 [210]	UPDRS, H&Y, off/dysk, LEDD, QoI	OUT (no UPDRS data in two appropriate time points or unclear data)	-	-	-	-
Vergani 2010 [211]	Safety	OUT (no UPDRS data)	-	-	–	-
Vesper 2007 [212]	UPDRS, H&Y, LEDD, safety	OUT (no UPDRS data in two appropriate time points / on med / on stim data)	-	-	-	-
Vingerhoets 1999 [213]	H&Y, LEDD	OUT (no UPDRS data)	-	-	-	-
Vingerhoets 2002 [214]	UPDRS, off/dysk, LEDD, safety	OUT (unclear measurement condition)	-	-	-	-
Visser-Vandewalle 2003 [215]	UPDRS, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Visser-Vandewalle 2005 [216]	UPDRS, off/dysk, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Voges 2006 [217]	Safety	OUT (no UPDRS data)	-	-	–	-
Volkmann 2009 [218]	UPDRS, off/dysk, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Walker 2009 [219]	UPDRS, off/dysk, LEDD, QoI, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Wang 2009 [220]	UPDRS	OUT (unclear data)	-	-	-	-
Weaver 2009 [221]	UPDRS, H&Y, off/dysk, LEDD, QoI, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-

Study	Initial selection	Final selection	Data included in analysis			
			UPDRS I	UPDRS II	UPDRS III	UPDRS IV
Weaver 2012 [222]	UPDRS, off/dysk, LEDD, Qol, safety	IN (NCT00056563 / NCT01076452 study)	✓	✓	✓	✓
Welter 2014 [223]	UPDRS, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Wenzelburger 2003 [224]	UPDRS, off/dysk, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Wider 2006 [225]	UPDRS, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Wider 2008 [226]	UPDRS, off/dysk, LEDD, safety	IN (with Aybek 2007)	✓	✓	✓	-
Williams 2010 [227]	UPDRS, off/dysk, LEDD, Qol, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Winkler 2013 [228]	LEDD	OUT (no UPDRS data)	-	-	-	-
Witjas 2007 [229]	UPDRS, H&Y, off/dysk, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Witt 2011 [230]	UPDRS, off/dysk, LEDD, Qol,	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Witt 2013 [231]	UPDRS, H&Y, LEDD	OUT (only baseline data for UPDRS III)	-	-	-	-
Yamada 2006 [232]	UPDRS, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Yamada 2007 [233]	UPDRS, off/dysk, LEDD,	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Yamada 2008 [234]	UPDRS, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Yamada 2009 [235]	UPDRS, LEDD, safety	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Yamada 2010 [236]	UPDRS, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Zahodne 2009 [237]	UPDRS, LEDD, Qol	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Zangaglia 2009 [238]	UPDRS, H&Y, LEDD	OUT (no UPDRS data in two appropriate time points)	-	-	-	-
Zibetti 2007 [239]	UPDRS, off/dysk, safety	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-
Zibetti 2009 [240]	UPDRS, LEDD	OUT (no UPDRS data in two appropriate time points / no on med / on stim data)	-	-	-	-

Off – off time, dysk – dyskinesia, LEDD – levodopa equivalent daily dose

Figure 2.
Overview of studies selection: PRISMA flowchart – long-term DBS effectiveness



A.2.3. Data extraction

Studies included in the analysis for particular UPDRS scores are listed in Table 27. Brief description of the studies is provided in Table 28.

Table 27
Long-term DBS effectiveness studies included in the analysis

Parameter	UPDRS I	UPDRS II	UPDRS III	UPDRS IV
Publications included	Weaver 2012 Gan 2007 / Gervais-Bernard 2009 Hung 2013 Janssen 2014 Kim 2013 Kishore 2010 Schupbach 2005 Wider 2008	Aviles-Olmos 2014 Weaver 2012 Gan 2007 / Gervais-Bernard 2009 Janssen 2014 Kim 2013 Kishore 2010 Krack 2003 Li 2013 Piboolnurak 2007 Romito 2009 Schupbach 2005 Wider 2008	Aviles-Olmos 2014 Aybek 2007 / Wider 2008 Fasano 2010 Weaver 2012 Gan 2007 / Gervais-Bernard 2009 Janssen 2014 Kim 2013 Kishore 2010 Krack 2003 Paek 2013 Piboolnurak 2007 Schupbach 2005 Toft 2011	Weaver 2012 Gan 2007 / Gervais-Bernard 2009 Hung 2013 Janssen 2014 Kim 2013 Merola 2014 Schupbach 2005
Total number of publications/studies	**9/8**	**13/12**	**15/13**	**8/7**

Table 28
Study characteristic – DBS long-term effectiveness

Study	Study design	Follow-up	No of patients	Baseline patients characteristics			
				Age [mean (SD)]	Duration of PD [years (SD)]	Hoehn & Yahr (SD)	LEDD [mg (SD)]
Aviles-Olmos 2014	**Design:** nonrandomized, prospective **Aim:** To report the long term outcome in a cohort of individuals who underwent STN DBS **Population:** United Kingdom	8 years	41	56.2 (8.4)	12.9 (5.8)	Not reported	1 471 (515)
Aybek 2007	**Design:** nonrandomized, prospective **Aim:** to evaluate the long-term cognitive profile and the incidence of dementia in a cohort of PD patients treated by STN-DBS **Population:** Switzerland	3 years	57	63.8 (8)	15.7 (5)	Not reported	1 097.5 (523.0)
Wider 2008	**Design:** nonrandomized, prospective, single center **Aim:** To describe the long-term outcome in advanced PD patients treated with STN-DBS. **Population:** Switzerland	5 years	50	64.9 (7.6)	14.4 (4.9)	Not reported	1128 (493)
Fasano 2010	**Design:** nonrandomized, prospective, single center **Aim:** To provides long-term assessment of patients who underwent STN-DBS **Population:** Italy	8 years Mean: 96 (3,1) months	20	56.9 (7.2)	13.7 (4.8)	≥3	1 418.2 (782.8)

Study	Study design	Follow-up	No of patients	Baseline patients characteristics			
				Age [mean (SD)]	Duration of PD [years (SD)]	Hoehn & Yahr (SD)	LEDD [mg (SD)]
Weaver 2012	**Design:** RCT, prospective, multicenter **Aim:** to compare long-term outcomes of DBS of GPi and STN for PD patients **Population:** USA	3 years	159	60.53 (8.57)	Not reported	OFF: 3.3 (0.8)	1323.18 (557.05)
Gan 2007	**Design:** RCT, prospective **Aim:** To assess the long-term efficacy and safety of STN-DBS in patients with advanced PD. **Population:** France	3 years	36	55.4 (8.3)	12.5 (4.0)	Not reported	1 228.3 (648.9)
Gervais-Bernard 2009	**Design:** RCT, prospective **Aim:** To assess the long-term efficacy and safety of STN-DBS in patients with advanced PD. **Population:** France	5 years	23	55.1 (7.2)	12.9 (3.2)	Not reported	1 188 (465)
Hung 2013	**Design:** nonrandomized, prospective **Aim:** Assessing which target symptoms have long-term effects from STN-DBS. **Population:** Taiwan.	7 years	120	49.5 (11.6)	9.8 (5.1)	3.3 (0.9)	779.1 (389.5)
Janssen 2014	**Design:** nonrandomized, observational, prospective, cohort study **Aim:** To provide an analysis of motor and cognitive outcome after STN DBS **Population:** Netherlands	Mean: 89.6 (40.6) months 10 years	26	58.0 (6.9)	12.7 (5.1)	Not reported	824 (479)
Kim 2013	**Design:** nonrandomized, prospective **Aim:** To analyze long-term follow-up data of STN DBS cases and to identify the factors related to outcomes **Population:** South Korea	7 years Mean: 57.48 months	52	57.60 (10.58)	10.25 (4.84)	3.07 (0.76)	957.16 (487.10)
Kishore 2010	**Design:** nonrandomized, prospective **Aim:** Assessing stability of effects of STN stimulation in PD **Population:** India	5 years	45	55.4 (10.9)	11.1 (5.7)	ON: 2.3 (0.5) OFF: 3.7 (0.9)	669.8 (359.7)
Krack 2003	**Design:** nonrandomized, prospective **Aim:** To report long-term outcomes of STN-DBS therapy. **Population:** France	5 years	49	55.0 (7.5)	14.6 (5.0)	Not reported	1 409 (605)
Li 2013	**Design:** nonrandomized, prospective **Aim:** To evaluate the outcome of bilateral STN stimulation to PD patients **Population:** China	8 years	31	53.5 (11.7)	7.86	Stage: 2-4	967.8 (381.3)

Study	Study design	Follow-up	No of patients	Baseline patients characteristics			
				Age [mean (SD)]	Duration of PD [years (SD)]	Hoehn & Yahr (SD)	LEDD [mg (SD)]
Merola 2014	**Design:** observational, nonrandomized, retrospective **Aim:** To analyze the role of PD-MCI in patients treated with STN-DBS **Population:** Italy	5 years	174	60.31 (6.72)	13.91 (4.75)	ON: 2.62 (0.81) OFF: 3.46 (0.99)	1 063.59 (409.73)
Paek 2013	**Design:** nonrandomized, retrospective **Aim:** to compare the long-term clinical outcomes of advanced PD patients following bilateral STN-DBS in terms of the positioning of their electrodes **Population:** South Korea	3 years	41	61.9 (7.9)	13.7 (4.1)	ON: 2.3 (0.7) OFF: 3.1 (1.0)	896.8 (423.7)
Piboolnurak 2007	**Design:** nonrandomized, prospective **Aim:** To evaluate changes in the l-dopa response over time in STN-DBS **Population:** Canada	5 years	33	53.4 (8.3)	13.5 (4.7)	Not reported	1 267.2 (521.2)
Romito 2009	**Design:** nonrandomized, prospective **Aim:** To reduce and stabilize dopaminergic medication after STN stimulation **Population:** Italy	5 years	20	56.4 (6.9)	14.3 (6.2)	ON: 2.6 (0.8) OFF: 4.4 (0.9)	1 457.6 (785.6)
Schupbach 2005	**Design:** nonrandomized, prospective **Aim:** To provides a follow up data of PD patients treated with stimulation of the STN **Population:** France	5 years	37	54.9 (9.1)	15.2 (5.3)	Median: 5 (4-5)	1 468 (811)
Toft 2011	**Design:** nonrandomized, retrospective, single center. **Aim:** To report long-term data of STN-DBS treatment efficacy and mortality **Population:** Norway	Mean: 3.3 years 5 years	144	60.3 (7.8)	11.0 (4.8)	Not reported	991 (462)

The data extracted from the studies included in the analysis is presented below (Table 29, Table 30, Table 31, Table 32).

Table 29.
DBS long-term effectiveness - UPDRS I – data extraction

Study	Publication(s)	Mean UPDRS I (no of patients)								
		Baseline	1 yrs.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	10 yrs.
Gan 2007 / Gervais-Bernard 2009	Gan 2007	1.30 (36)	1.70 (36)	N/D	2.40 (36)	N/D	N/D	N/D	N/D	N/D
	Gervais-Bernard 2009	0.83 (23)	1.48 (23)	N/D	N/D	N/D	2.57 (23)	N/D	N/D	N/D
Hung 2013		4.60 (120)	2.90 (88)	2.90 (60)	N/D	N/D	3.30 (31)	N/D	3.80 (17)	N/D
Kim 2013		3.60 (52)	2.90 (52)	2.90 (52)	3.20 (52)	3.60 (<52)[a]	4.40 (<52)[a]	4.50 (<52)[a]	3.00 (<52)[a]	N/D
Kishore 2010		1.30 (45)	1.30 (45)	N/D	1.20 (36)	N/D	2.10 (29)	N/D	N/D	N/D
Weaver 2012		2.79 (159)	N/D	2.88 (157)	3.23 (159)	N/D	N/D	N/D	N/D	N/D
Schupbach 2005		2.30 (37)	N/D	2.00 (32)	N/D	N/D	3.30 (30)	N/D	N/D	N/D
Janssen 2014		1.80 (26)	1.40 (26)	N/D	N/D	N/D	3.10 (18)	N/D	N/D	4.20 (12)
Wider 2008		1.80 (37)	N/D	2.60 (36)	N/D	N/D	3.70 (37)	N/D	N/D	N/D

a) exact number of patients not reported (for the purposes of the analysis 52 assumed at all time points)

Table 30.
DBS long-term effectiveness - UPDRS II (on med / on stim) – data extraction

Study	Publication(s)	Mean UPDRS II (no of patients)									
		Baseline	1 yrs.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	10 yrs.
Aviles-Olmos 2014		6.20 (41)	7.50 (41)	N/D	N/D	N/D	13.20 (41)	N/D	N/D	15.20 (12)	N/D
Gan 2007 / Gervais-Bernard 2009	Gan 2007	4.50 (36)	8.50 (36)	N/D	10.40 (36)	N/D	N/D	N/D	N/D	N/D	N/D
	Gervais-Bernard 2009	4.70 (23)	7.65 (23)	N/D	N/D	11.35 (23)	N/D	N/D	N/D	N/D	N/D
Krack 2003		7.30 (49)	7.40 (43)	N/D	10.70 (40)	N/D	14.00 (39)	N/D	N/D	N/D	N/D
Kim 2013		14.63 (52)	10.15 (52)	10.30 (52)	10.70 (52)	11.10 (<52)[a]	12.50 (<52)[a]	12.80 (<52)[a]	12.70 (<52)[a]	N/D	N/D

Study	Publication(s)	Mean UPDRS II (no of patients)									
		Baseline	1 yrs.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	10 yrs.
Kishore 2010		9.50 (49)	5.90 (45)	N/D	7.30 (36)	N/D	7.10 (29)	N/D	N/D	N/D	N/D
Li 2013		8.80 (31)	6.40 (31)	N/D	N/D	N/D	10.90 (31)	N/D	N/D	16.70 (29)	N/D
Weaver 2012		18.92 (159)	N/D	14.97 (155)	17.50 (157)	N/D	N/D	N/D	N/D	N/D	N/D
Piboolnurak 2007		11.20 (33)	N/D	N/D	13.20 (33)	N/D	14.60 (17)	N/D	N/D	N/D	N/D
Romito 2009		10.90 (20)	7.50 (20)	N/D	8.90 (20)	N/D	8.60 (20)	N/D	N/D	N/D	N/D
Schupbach 2005		11.50 (37)	N/D	10.00 (32)	N/D	N/D	14.30 (30)	N/D	N/D	N/D	N/D
Janssen 2014		11.30 (26)	8.60 (23)	N/D	N/D	N/D	14.30 (18)	N/D	N/D	N/D	20.40 (12)
Wider 2008		10.00 (37)	N/D	12.80 (36)	N/D	N/D	18.90 (37)	N/D	N/D	N/D	N/D

a) exact number of patients not reported (for the purposes of the analysis 52 assumed at all time points)

Table 31.
DBS long-term effectiveness - UPDRS III (on med / on stim) – data extraction

Study	Publication(s)	Mean UPDRS III (no of patients)									
		Baseline	1 yrs.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	10 yrs.
Aviles-Olmos 2014		14.00 (41)	14.00 (41)	N/D	N/D	N/D	23.90 (41)	N/D	N/D	28.70 (12)	N/D
Fasano 2010		24.50 (20)	21.30 (20)	N/D	22.90 (20)	N/D	21.40 (20)	N/D	N/D	26.90 (20)	N/D
Gan 2007 / Gervais-Bernard 2009	Gan 2007	14.10 (36)	12.50 (36)	N/D	12.50 (36)	N/D	N/D	N/D	N/D	N/D	N/D
	Gervais-Bernard 2009	14.83 (23)	10.34 (23)	N/D	N/D	N/D	13.17 (23)	N/D	N/D	N/D	N/D
Krack 2003		14.30 (49)	11.40 (43)	N/D	15.30 (40)	N/D	21.10 (39)	N/D	N/D	N/D	N/D
Kim 2013		21.70 (52)	17.00 (52)	17.70 (52)	18.50 (52)	18.50 (<52)[a]	22.10 (<52)[a]	21.80 (<52)[a]	22.10 (<52)[a]	N/D	N/D
Kishore 2010		16.20 (45)	13.90 (45)	N/D	14.70 (36)	N/D	16.50 (29)	N/D	N/D	N/D	N/D
Weaver 2012		21.26 (159)	N/D	19.43 (146)	21.96 (143)	N/D	N/D	N/D	N/D	N/D	N/D
Paek 2013		19.20 (41)	15.00 (41)	14.20 (41)	19.50 (41)	N/D	N/D	N/D	N/D	N/D	N/D

Study	Publication(s)	Mean UPDRS III (no of patients)									
		Baseline	1 yrs.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	10 yrs.
Piboolnurak 2007		22.40 (33)	N/D	N/D	23.00 (33)	N/D	24.80 (17)	N/D	N/D	N/D	N/D
Schupbach 2005		17.80 (37)	N/D	10.10 (32)	N/D	N/D	17.90 (30)	N/D	N/D	N/D	N/D
Janssen 2014		21.20 (26)	13.00 (26)	N/D	N/D	N/D	21.70 (18)	N/D	N/D	N/D	28.70 (12)
Toft 2011		13.20 (131)	12.50 (131)	15.40 (110)	18.10 (89)	19.50 (52)	22.40 (32)	N/D	N/D	N/D	N/D
Wider / Aybek study	Aybek 2007	22.70 (43)	N/D	N/D	25.10 (43)	N/D	N/D	N/D	N/D	N/D	N/D
	Wider 2008	24.30 (37)	N/D	27.70 (36)	N/D	N/D	30.60 (37)	N/D	N/D	N/D	N/D

a) exact number of patients not reported (for the purposes of the analysis 52 assumed at all time points)

Table 32.
DBS long-term effectiveness - UPDRS IV – data extraction

Study	Publication(s)	Mean UPDRS IV (no of patients)								
		Baseline	1 yrs.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	10 yrs.
Gan 2007 / Gervais-Bernard 2009	Gan 2007	9.00 (36)	1.90 (36)	N/D	3.10 (36)	N/D	N/D	N/D	N/D	N/D
	Gervais-Bernard 2009	8.30 (23)	1.24 (23)	N/D	N/D	N/D	3.26 (23)	N/D	N/D	N/D
Hung 2013		5.50 (120)	1.70 (88)	1.80 (60)	N/D	N/D	1.90 (31)	N/D	1.80 (17)	N/D
Kim 2013		7.63 (52)	4.10 (52)	4.40 (52)	4.60 (52)	4.80 (<52) [a]	6.00 (<52) [a]	6.40 (<52) [a]	5.40 (<52) [a]	N/D
Merola 2014		8.03 (174)	2.20 (174)	N/D	2.72 (174)	N/D	3.32 (174)	N/D	N/D	N/D
Weaver 2012		9.03 (157)	N/D	4.56 (122)	4.21 (124)	N/D	N/D	N/D	N/D	N/D
Schupbach 2005		12.70 (37)	N/D	3.20 (32)	N/D	N/D	5.10 (30)	N/D	N/D	N/D
Janssen 2014		7.20 (26)	1.50 (26)	N/D	N/D	N/D	2.40 (18)	N/D	N/D	2.30 (12)

a) exact number of patients not reported (for the purposes of the analysis 52 assumed at all time points)

A.3. Long-term progression in BMT studies

A.3.1. Search strategy

In order to identify data on long-term progression of UPDRS outcomes (for modelling of "natural disease progression") a systematic search of "BMT" studies was performed in Medline (via PubMed). "BMT" was defined as any medical intervention (except DBS, CSAI, CDLCI), and intervention studies of PD medication, or population-based studies, were included. The search in Medline database was performed on 12th February 2015. The search was performed in the initial phase of the project, when model structure and data included in the analysis were unknown. Therefore, broad inclusion criteria were defined (details in Table 34).

An additional non-systematic search via google and in ISPOR database [241] was done. As this was non-systematic no specific strategy was used.

Table 33.
Search strategy in Medline database – natural disease progression

Search	Search terms	Results
#6	#4 AND #5	578
#5	longterm OR long-term OR "long term" OR natural OR progress OR progression OR decline OR history OR course OR predict OR prediction OR fall OR advancement OR evolution OR evolve OR transition	3,570,509
#4	#1 AND #2 AND #3	1,502
#3	UPDRS OR "Unified Parkinson's Disease Rating Scale" or (Hoehn and (Yahr's or Yahr)) OR PDQ OR "Parkinson's Disease Questionnaire" OR EuroQol OR EQ5D OR EQ-5D OR "EQ 5D"	9,424
#2	epidemiol* OR cross-section OR cross-sectional OR "cross sectional" OR register OR population-based OR prospective OR retrospective OR registry OR registries OR observational OR longitudinal OR database	2,843,637
#1	(Parkinson's disease) OR ("Parkinson Disease"[Mesh]) OR (Parkinson*) OR (parkinsonism OR (parkinsonian syndrome)) OR (paralysis agitans)	96,372
Search strategy executed on 12th February 2015		

A.3.2. Study selection

All studies identified within search process were initially assessed based on title and abstracts. Papers not meeting predefined inclusion criteria as indicated by title and abstracts were excluded.

A summary of primary selection criteria is presented in Table 34.

Table 34.
Selection criteria for studies on Parkinson's Disease progression in BMT treated patients

Criterion	Inclusion	Exclusion
Population	• Patients with Parkinson's Disease	• Other disease
Intervention	• Any medical intervention (except those listed in exclusion criteria); if specific intervention assessed, study included only if results reported in the period beyond first two years from treatment initiation	• DBS, CSAI, CDLCI

Data type	• Disease severity / progression measured as:
	  • *UPDRS,*
	  • *H&Y,*
	  • *QoL change (PDQ-39, EQ-5D)*
	  • *off time, motor complications occurrence, dyskinesias severity, etc.*
	• Data reported as:
	  • *annual change in parameter value,*
	  • *probability of progression / transition between health states,*
	  • *any data allowing to calculate progression rate within time*
		• Lack of data specified in inclusion criteria

Study design	• Any type of study	-
Publication date	• Not relevant (up to date of search – 12th February 2015)	-

Data from 36 publications were included after full text analysis based on selection criteria. At this stage of the search, references of the retrieved publications were also checked and a non-systematic search was done (Table 36). As a result, 30 additional papers were included.

For the purposes of economic analysis, additional selection was done and only studies reporting data on UPDRS progression were finally included. Additional selection criteria, in order to have data to derive UPDRS progression rates, were:

- UPDRS scores measured ON-meds,
- at least 2-year follow-up (excluding initial period of treatment – if specific intervention assessed, first 2 years of treatment excluded from the analysis – to eliminate short-term effectiveness),
- studies performed in early / recently diagnosed PD patient were excluded (the exception is Reinosso 2014 study [242] – performed in recently diagnosed PD patients, but results reported separately for period 7-9 years from diagnosis).

A brief summary of the search and results of study selection is presented in Table 35 and Table 36.

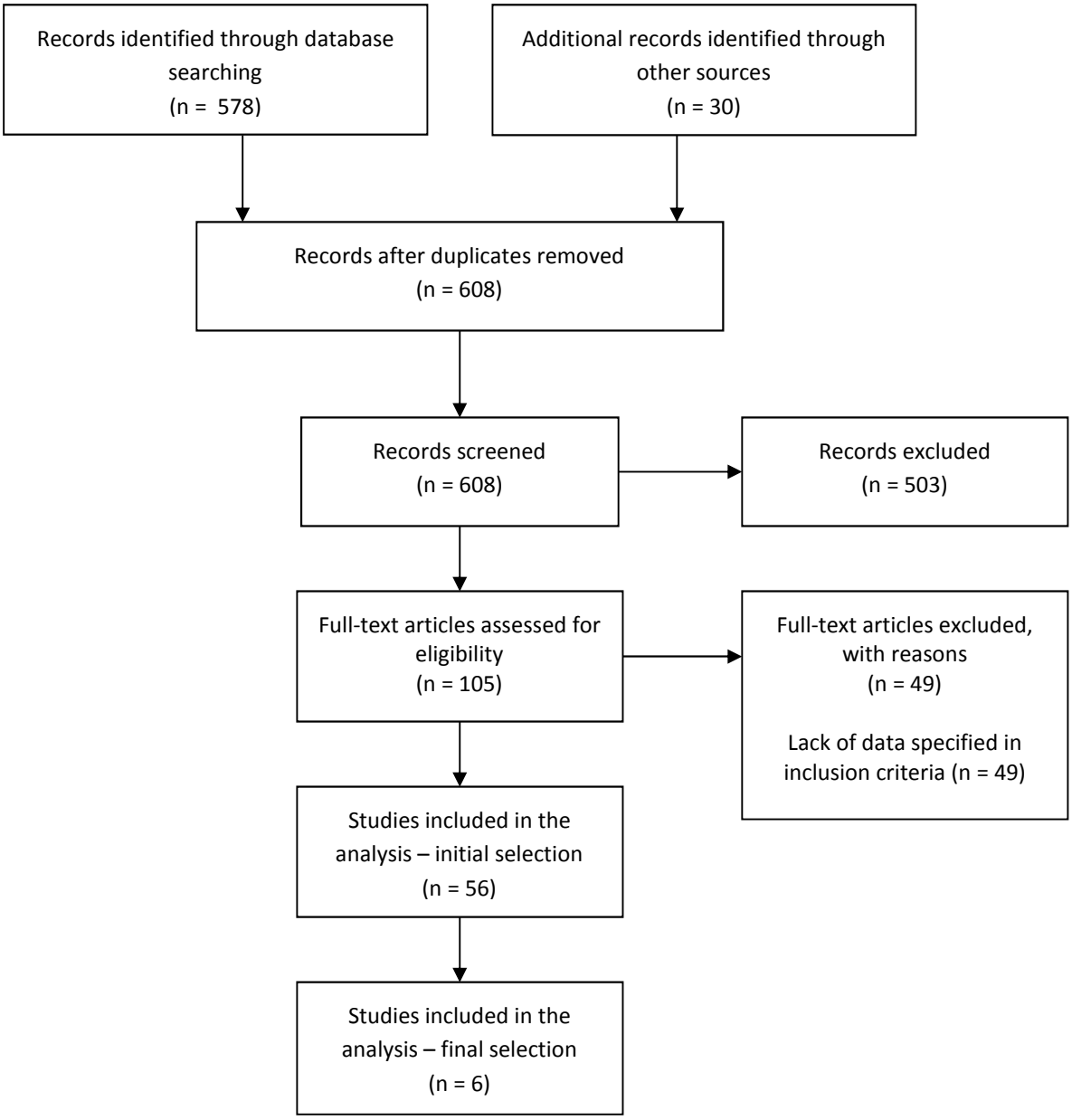
Table 35.
Summary of systematic search for PD progression in BMT treated patients

Search date	Database	No. of abstracts returned	Initial selection		Final no. of included studies
			No. included in full text analysis	No. of included studies	
12th February 2015	Pubmed	578	75	36	5

Table 36
Summary of systematic search for PD progression in BMT treated patients – Additional search

Data source	No. of considered studies (initial selection)	Final no. of included studies
References of the retrieved publications	24	1
Other (google, ISPOR)	6	0

Figure 3.
Overview of studies selection: PRISMA flowchart – long-term progression in BMT studies



No data for UPDRS IV progression were identified. The studies included in the final analysis for UPDRS I-III are listed in Table 37.

Table 37
Parkinson's Disease progression in BMT treated patients in final analysis

Parameter	Disease progression measured by:			
	UPDRS I	**UPDRS II**	**UPDRS III**	**UPDRS IV**
Publications included	Jankovic 2001 [243]	Alves 2005 [244] Jankovic 2001 [243] Le Witt 2013 [245]	Alves 2005 [244] Jankovic 2001 [243] Le Witt 2013 [245] Reinosso 2014 [242] Brooks 2008 [246] Schrag 2007 [247]	-
Total number of publications / studies	**1**	**3**	**6**	**0**

The publications included after initial selection, but finally excluded from the analysis are listed in Table 38.

Table 38.
Studies on BMT progression not included in final calculation

Publication	Reason for exclusion
Antonini 2012 [248]	population of early PD
Bloem 2001 [249]	no data on UPDRS progression
Chan 2007 [250]	data on total UPDRS only
Cheng 2014 [251]	no data on UPDRS progression
Chia 1992 [252]	no data on UPDRS progression
Di Rocco 1996 [253]	no data on UPDRS progression
Duarte 2015 [254]	not enough data for calculation
Evans 2011 [255]	no data on UPDRS progression
Factor 2001 [256]	short follow-up
Foltynie 2004 [257]	no data on UPDRS progression
Gago 2009 [258]	not enough data for calculation
Gazibara 2014 [259]	no data on UPDRS progression
Goetz 1988 [260]	no data on UPDRS progression
Guimaraes 2005 [261]	not enough data for calculation
Hauser 2006 [262]	no data on UPDRS progression
Hauser 2007 [263]	not enough data for calculation
Hely 1999 [264]	no data on UPDRS progression
Hely 2005 [265]	no data on UPDRS progression
Hiorth 2013 [266]	no data on UPDRS progression
Hiorth 2014 [267]	no data on UPDRS progression
Hoehn 1983 [268]	no data on UPDRS progression
Holford 2006 [269]	data on total UPDRS only
Janssen 2014 [118]	DBS study

Publication	Reason for exclusion
Johnson 2013 [270]	no data on UPDRS progression
Johnson 2013 [271]	no data on UPDRS progression
Klotsche 2011 [272]	not enough data for calculation
Lang 2013 [273]	modified UPDRS
Larsen 1999 [274]	early PD
Lindholm 2015 [275]	no data on UPDRS progression
Liou 2008 [276]	no data on UPDRS progression
Lopez 2010 [277]	population of early PD
Matinolli 2011 [278]	no data on UPDRS progression
Muller 2000 [279]	no data on UPDRS progression
Pickering 2007 [280]	no data on UPDRS progression
Poewe 2006 [281]	no data on UPDRS progression
Rajput 2009 [282]	no data on UPDRS progression
Rascol 2000 [283]	early PD
Roos 1996 [284]	no data on UPDRS progression
Rudzinska 2008 [285]	no data on UPDRS progression
Rudzinska 2013 [286]	no data on UPDRS progression
Rudzinska 2013 [287]	no data on UPDRS progression
Sato 2006 [288]	no data on UPDRS progression
Schrag 2000 [289]	no data on UPDRS progression
Schrag 2009 [290]	short follow-up
Stocchi 2002 [291]	data on graph. hard to read in details
Velseboer 2013 [292]	no data on UPDRS progression
Vu 2012 [293]	not enough data for calculation
Williams-Gray 2013 [294]	no data on UPDRS progression
Zhao 2010 [295]	no data on UPDRS progression
Zhao 2011 [296]	no data on UPDRS progression

A.3.3. Data extraction

Brief description of the studies included in the analysis is provided in Table 39.

Table 39
Study characteristic – BMT long-term progression

Study		Study design	Follow-up	No of patients	Baseline patients characteristics		
					Age [mean (SD)]	Duration of PD [years (SD)]	Hoehn & Yahr (SD)
Alves 2005		**Design:** nonrandomized, prospective, **Aim:** To investigate risk factors and the rate of progression of motor symptoms and disability in a population-based cohort of patients with PD. **Population:** Norway	8 years	232	73.5 (8.5)	9.1 (5.7)	2.8 (1.1)
Brooks 2008		**Design:** retrospective, pooled data from four studies **Aim:** To evaluate the efficacy and safety of long-term levodopa/DDCI and entacapone therapy in patients with PD **Population:** As in four analyzed studies	5 years	649	63.1 (9.4)	9.5 (5.2)	2.4 (0.7)
Jankovic 2001		**Design:** prospective, single center **Aim:** To determine the overall rate of functional decline and to assess the progression of different signs of PD **Population:** Texas/USA	6.36 years	297	55.1	6.5	Not reported
Le Witt 2013	**SP516**	**Design:** open-label extension of RCT studies, prospective **Aim:** To evaluate the safety, tolerability and efficacy of the dopaminergic agonist, rotigotine, in patients with advanced PD. **Population:** 19 countries (17 in SP 516, and 2 in SP 715	Up to 4 years	395	64.4 (9.2)	8.5 (4.6)	Not reported
	SP715		up to 6 years	258	66.4 (9.6)	7.8 (4.5)	
Reinoso 2014		**Design:** retrospective **Aim:** To understand the natural clinical evolution of treated PD patients and to identify the variables that predict greater progression in these patients. **Population:** Singapore	9 years	576	63.67 (10.39)	Not reported	2.13 (0.69)
Schrag 2007		**Design:** nonrandomized, prospective **Aim:** To assess the rate of clinical progression of PD **Population:** United Kingdom	4 years	124	Not reported	Not reported	2.2 (1.0)

The data extracted from the studies included in the analysis is presented in Table 40.

Table 40.
Long-term UPDRS progression – data extraction

Study	UPDRS change [points per year]				Note
	I	II	III	IV	
Alves 2005	-	1.900	3.300	-	General PD group; data reported directly in publication
Brooks 2008	-	-	1.000	-	Patients from clinical study treated with entacapone; data reported directly within study; value refers to period when initial improvement run out
Jankovic 2001	0.167	0.560	0.704	-	General PD group; data reported directly in publication
LeWitt 2013	-	1.799	1.967	-	Patients from clinical studies treated with levodopa or rotigotine; baseline value (since disease start progress and at the end of follow-up) taken from graph; annual change for 2 groups calculated and then averaged
Reinosso 2014	-	-	2.120	-	Data from period 7-9 years after treatment initiation; data reported directly in publication
Schrag 2000	-	-	0.378	-	Data from clinic based group with Hoehn&Yahr score 3-5; in study percentage change was reported (0.35%) and here is transformed into point change (0.35% x 108 [UPDRS III range])

Final model assumptions are presented in section B.2.

A.4. Mortality

A.4.1. Search strategy

In order to identify data on mortality in PD patients Medline database (via PubMed) was systematically searched. Search was performed in two steps:

1. Firstly, other systematic reviews were identified;
2. Secondly, a systematic search was done in order to identify studies publicized after date of search in latest review identified in step 1.

Detailed search strategy for other systematic reviews is presented in Table 41. This search was done on 25th March 2015.

Table 41.
Search strategy for mortality data in Medline database – systematic reviews

Search	Query	Items found
#5	(#1 AND #2 AND #3) AND “systematic review”	30
#4	#1 AND #2 AND #3	1432
#3	epidemiol* OR cross-section OR cross-sectional OR "cross sectional" OR register OR population-based OR prospective OR retrospective OR registry OR registries OR observational OR longitudinal OR database	2873113
#2	mortality OR survival OR death	1826331

Search	Query	Items found
#1	(Parkinson's disease) OR ("Parkinson Disease"[Mesh]) OR (Parkinson*) OR (parkinsonism OR (parkinsonian syndrome)) OR (paralysis agitans)	97201
	Search strategy executed on 25th March 2015	

Out of 30 abstracts identified in the search, 2 publications (describing systematic reviews) were included in full text analysis [297, 298]. The latest systematic review identified was performed by MacLeod 2014. As MacLeod 2014 review was also more comprehensive than the second systematic review identified [297], only MacLeod 2014 review was included in the analysis. Detailed methodology and search strategy used by MacLeod 2014 is presented in the publication.

As the date of last search in MacLeod 2014 review was October 2012, we did an additional search in order to identify other studies published after this date. In order to minimize possible search bias a limitation for studies published since January 2012 was done. Search strategy is presented in Table 42. The date of this search was 23th April 2015. Additionally, a non-systematic search via google was done.

Table 42.
Search strategy for mortality data in Medline database – primary studies

Search	Query	Items found
#5	(#1 AND #2 AND #3) Filters: Publication date from 2012/01/01	348
#4	#1 AND #2 AND #3	1443
#3	epidemiol* OR cross-section OR cross-sectional OR "cross sectional" OR register OR population-based OR prospective OR retrospective OR registry OR registries OR observational OR longitudinal OR database	2894977
#2	mortality OR survival OR death	1837299
#1	(Parkinson's disease) OR ("Parkinson Disease"[Mesh]) OR (Parkinson*) OR (parkinsonism OR (parkinsonian syndrome)) OR (paralysis agitans)	97726
	Search strategy executed on 23th April 2015	

A.4.2. Study selection

All studies identified within the Medline database search (studies published from 2012 onwards) were first analysed based on predefined selection criteria described in Table 43.

Once model structure was decided selection criteria were narrowed to include only studies examining association between UPDRS and mortality rate. At this stage, the studies included in MacLeod 2014 review were analysed. The information provided in MacLeod 2014 review allowed to identify relevant studies (assessing dependence between UPDRS and mortality), and so the study selection was based on information provided in MacLeod 2014 review. Similarly, an additional non-systematic

search via google was aimed at identifying only studies assessing relationship between UPDRS and mortality.

Table 43.
Selection criteria for studies on mortality data

Criterion	Inclusion	Exclusion
Population	• Patients with Parkinson's disease	• Other
Data type	• Data allowing to calculate mortality during treatment with one of following intervention: DBS, BMT, CSAI, CDLCI. • Data allowing for determining relationship between mortality and progression assessed with one of following: H&Y, UPDRS. • Data allowing to calculate mortality in general with PD.	• Lack of data specified in inclusion criteria.
Study design	• Observational studies, • Registries.	• RCT studies, • Case series.
Publication date / other criteria	• Not relevant (up to date of the search - 23th April 2015) • Publicized in English	–

A brief summary of additional search is presented in Table 44.

Table 44.
Summary of systematic search for mortality data – additional search

Data source	No. of abstracts returned	Initial selection		Final no. of included studies
		No. included in full text analysis	No. of included studies	
Medline (additional search)	348	43	18	0

Details on selection of studies included in MacLeod 2014 review are presented in Table 45.

Table 45.
Summary of systematic search for mortality data – studies included in MacLeod 2014 review

Data source	No. of studies included in the review	No. included in full text analysis	Final no. of included studies
MacLeod 2014 review	88 unique studies described in 176 publications	3[a]	2

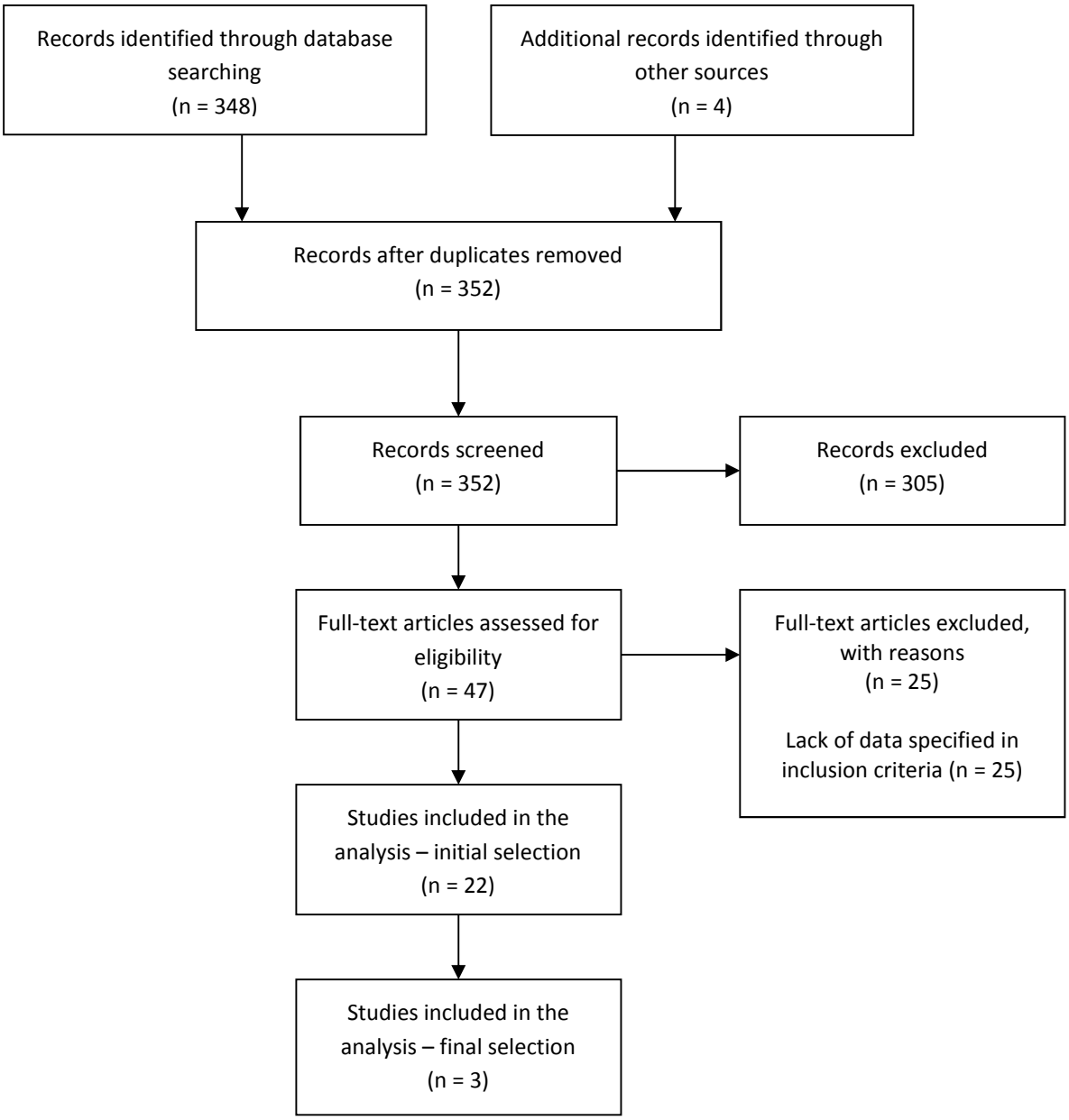
a) only publications reporting information on relationship between UPDRS and mortality (as indicated by information provided in MacLeod 2014 review) were included

Additionally one study was identified in non-systematic search via google and this study was also included in the analysis [299].

The diagram below (Figure 4) provides information on selection process for:

- 3 publications (out of 176) included in MacLeod 2014 review, that were selected for full text analysis based on information provided in MacLeod 2014 review,
- 348 publications identified through additional search in Pubmed (via Medline), to identify studies published after MacLeod 2014.,
- 1 publication identified in non-systematic search via google.

Figure 4.
Overview of studies selection: PRISMA flowchart – mortality data



List of publications finally included in the analysis is presented in Table 46.

Table 46
Studies reporting association between UPDRS and mortality included in final analysis

Parameter	Mortality
Publications included	Marras 2005 [300], Forsaa 2010 [301], Skorvanek 2013 [299]
Total number of publications	**3**

List of publications included after initial selection, but finally excluded from the analysis is presented in Table 47.

Table 47.
Studies on mortality not included in final calculation (included after initial selection)

Publication	Reason of exclusion
Jones 2012 [302]	association between UPDRS and mortality not examined in the study
Auyeung 2012 [303]	association between UPDRS and mortality not examined in the study
Benito-Leon 2014 [304]	association between UPDRS and mortality not examined in the study
Chillag-Talmor 2013 [305]	association between UPDRS and mortality not examined in the study
Desesquelles 2014 [306]	association between UPDRS and mortality not examined in the study
Duarte 2013 [307]	association between UPDRS and mortality not examined in the study
Duarte 2015 [254]	association between UPDRS and mortality not examined in the study
Frandsen 2014 [308]	association between UPDRS and mortality not examined in the study
Hobson 2010 [309]	association between UPDRS and mortality not examined in the study
Hoyert 2012 [310]	association between UPDRS and mortality not examined in the study
Kaltenboeck 2012 [311]	association between UPDRS and mortality not examined in the study
Mackenbach 2014 [312]	association between UPDRS and mortality not examined in the study
Merola 2014 [149]	association between UPDRS and mortality not examined in the study
Morgan 2014 [313]	association between UPDRS and mortality not examined in the study
Oosterveld 2015 [314]	association between UPDRS and mortality examined, but reported results not useful for current analysis purposes
Peretz 2014 [315]	association between UPDRS and mortality not examined in the study
Vu 2012 [293]	association between UPDRS and mortality examined, but only total UPDRS or UPDRS II considered, whereas in the model only association between UPDRS III and mortality was taken into account (as most commonly reported)
Williams-Gray 2013 [294]	association between UPDRS and mortality not examined in the study
Willis 2012 [316]	association between UPDRS and mortality not examined in the study

A.4.3. Data extraction

Studies finally included in the analysis together with data extracted from the studies are presented in Table 48.

Table 48
Association between UPDRS III and mortality – data extraction

Study	No of patients	Hazard ratio per 10 points increase	Comment
Marras 2005	800	1.30	associations between baseline variables of interest and time to death
Forsaa 2010	230	1.25	associations between variables with mortality adjustment for age
Skorvanek 2013	153	1.48	only poster for this study was available

Final model assumptions are presented in section B.7.

APPENDIX B. DATA ANALYSES FOR MODEL INPUT

B.1. CSAI and CDLCI short-term effectiveness (first 2 years in the model)

The following sections present detailed information on the analysis of CSAI and CDLCI short-term effectiveness data (UPDRS) that was performed to derive values for short-term effectiveness parameters (first 2 years in the model) included in the CE model for these therapies. Data included in the analyses are from studies identified in the systematic review of both therapies (details in section A.1).

B.1.1. CSAI

UPDRS I

The Drapier 2012 study indicates a 17% improvement with CSAI in part I of the UPDRS scale after 1 year of treatment vs baseline.

Table 49.
CSAI effectiveness– UPDRS I – data included in the analysis

Study	Baseline score (no of patients)	Percentage change vs baseline (no of patients)
		1 year
Drapier 2012	2.90 (23)	-17.24% (23)

The Drapier 2012 study is the only study reporting results (only after 1 year of CSAI treatment) for mentation, behaviour, and mood section of UPDRS. Thus, validation of its result and assessment of effectiveness of CSAI at other time points is not possible. In economic analysis it was conservatively assumed that improvement in UPDRS I score is seen immediately after treatment initiation and is maintained for 2 years of treatment (year 1 data used to populate CE model). The final model assumptions are presented in Table 50.

Table 50.
CSAI effectiveness – UPDRS I – CE model assumptions

Parameter	Treatment initiation		Year 1		Year 2		Source
	Mean	SE	Mean	SE	Mean	SE	
UPDRS I – percentage change from baseline	-17.24%	3.92%	-17.24%	3.92%	-17.24%	3.92%	Drapier 2012

UPDRS II

The Drapier 2012 study indicates a 8% worsening with CSAI in part II of the UPDRS scale after 1 year of treatment vs baseline.

Table 51.
CSAI effectiveness– UPDRS II – data included in the analysis

Study	Baseline score (no of patients)	Percentage change vs baseline (no of patients)
		1 year
Drapier 2012	10.20 (23)	7.84% (23)

Drapier 2012 study is the only one study reporting results (only after 1 year of CSAI treatment) for the activities of daily living section of UPDRS. Thus, validation of its result and assessment of effectiveness of CSAI at other time points is not possible. In economic analysis it was conservatively assumed that there is no immediate change in UPDRS II score after treatment initiation and percentage change after 2 years of treatment is the same as after the first year. The final model assumptions are presented in Table 52.

Table 52.
CSAI effectiveness – UPDRS II – CE model assumptions

Parameter	Treatment initiation		Year 1		Year 2		Source
	Mean	SE	Mean	SE	Mean	SE	
UPDRS II – percentage change from baseline	0.00%	0.00%	7.84%	3.78%	7.84%	3.78%	Drapier 2012

UPDRS III

CSAI effectiveness data on the UPDRS part III scale were reported in 3 studies – results after 1 year and 2 years of treatment are available Data on percentage changes in the UPDRS III vs baseline calculated from these studies are presented in Table 53.

Table 53.
CSAI effectiveness– UPDRS III – data included in the analysis

Study	Baseline score (no of patients)	Percentage change vs baseline (no of patients)	
		1 year	2 years
Drapier 2012	18.30 (23)	19.1% (23)	-
de Gaspari 2006	19.50 (13)	-1.3% (13)	-
Todorowa 2013	33.00 (20)	-	-56.1% (15)

Results of the included studies are not consistent. Two of them indicate that there is no improvement / only slight improvement after first year of treatment, while results of third study show significant improvement after 2 years of treatment. A possible explanation for this observation might be the different baseline levels of UPDRS III scores. The results of the Kanovsky 2002 study [16], showing an 45% improvement in UPDRS motor score after 6 months of treatment up to 2 years in patients with average baseline UPDRS III score of 29.7, support the conclusion that higher effectiveness is reached in more advanced patients. As no information about UPDRS measurement condition (on or off meds) was provided in Kanovsky 2002, this study was excluded from the quantitative analysis.

Finally, in economic analysis only data from Todorowa 2013 were used. It was conservatively assumed that improvement in UPDRS III score is seen immediately after treatment initiation and is maintained for 2 years of treatment (year 2 data used to populate CE model). The final model assumptions are presented in Table 54.

Table 54.
CSAI effectiveness – UPDRS III – CE model assumptions

Parameter	Treatment initiation		Year 1		Year 2		Source
	Mean	SE	Mean	SE	Mean	SE	
UPDRS III – percentage change from baseline	-56.1%	2.35%	-56.1%	2.35%	-56.1%	2.35%	Todorowa 2013

UPDRS IV

CSAI effectiveness data on the UPDRS part IV scale were reported in 5 studies and data for 3 time points are available. Data on percentage changes in the UPDRS IV vs baseline calculated from these studies are presented in Table 55.

Table 55.
CSAI effectiveness– UPDRS IV – data included in the analysis

Study	Baseline score (no of patients)	Percentage change vs baseline (no of patients)		
		6 months	1 year	2 years
Drapier 2012	7.70 (23)	-	-10.4% (23)	-
Kanovsky 2002	10.80 (12)	-50.0% (12)	-50.9% (12)	-50.0% (12)
Martinez-Martin 2011	10.00 (17)	-	-64.7% (17)	-
Martinez-Martin 2014	10.02 (43)	-40.8% (43)	-	-
Todorowa 2013	11.30 (20)	-	-	-54.0% (15)

All studies reported improvement in UPDRS IV score in all time points considered. For the purposes of CE model, the effectiveness was estimated as follows:

1. The weighted average % change at 1 year of treatment vs baseline (the most commonly considered time point in studies included in the analysis) was calculated based on the results of 3 studies reporting respective data – 37.50%.
2. The Kanovsky 2002 study was the only study with more than one time point and so results of this study were used to calculate the % change at 2 years of treatment relative to year 1 – 1.89% worsening after 2 years when compared to year 1 results (details in Table 56):

Table 56.
CSAI effectiveness – UPDRS IV – relative effectiveness (1 year vs 2 years) data

Study	Parameter	Baseline (no of patients)	1 year (no of patients)	2 years (no of patients)
Kanovsky 2002	Mean value	10.80 (12)	5.30 (12)	5.40 (12)
	% change	-	-	1.89% (vs 1 year)

The estimated weighted average % change vs baseline at 1 year of treatment (-37.50%) and the % change at 2 years relative to year 1 (1.89% worsening) were combined to calculate the % change at 2 years of treatment vs baseline – -36.22% [(1 - 0.37.5%) x (1 + 1.89%) – 1].

3. No data on initial effectiveness (immediately after treatment initiation) were identified. The results of 2 studies included in the analysis show that improvement in UPDRS IV is achieved as soon as after 6 months of treatment (see Table 55). It was conservatively assumed that initial effectiveness is the same as after first year of treatment.

The final model assumptions are presented in Table 57.

Table 57.
CSAI effectiveness – UPDRS IV – CE model assumptions

Parameter	Treatment initiation		Year 1		Year 2		Sources
	Mean	SE	Mean	SE	Mean	SE	
UPDRS IV – percentage change from baseline	-37.50%	3.86%	-37.50%	3.86%	-36.32%	1.47%	Drapier 2012 Kanovsky 2002 Martinez-Martin 2011

B.1.2. CDLCI

UPDRS I

CDLCI effectiveness data on the UPDRS part I scale were reported in 2 studies. Only results after 1 year of treatment were available, for which percentage changes to baseline were calculated (Table 58).

Table 58.
CDLCI effectiveness– UPDRS I – data included in the analysis

Study	Baseline score (number of patients)	Percentage change vs baseline (no of patients)
		1 year
Fernandez 2014[a]	2.20 (288)	0.00% (272)
Olanov 2014 / Slevin 2015[b]	1.80 (36)	16.7% (33)
Olanov 2014 / Slevin 2015[c]	1.80 (33)	38.9% (26)

a) In Fernandez 2014 number of patients not reported at 1 year time point for UPDRS I data, number of patients with UPDRS I data assumed the same as number of patients with completed 1 year of follow-up – 272;
b) patients randomized to CDLCI at baseline who continued CDLCI treatment for 12 + 52 weeks (baseline score based on baseline data, 12 + 52 weeks follow-up data used as proxy for 1 year results);
c) patients randomized to BMT at baseline who started CDLCI after 12 weeks and continued CDLCI for further 52 weeks (baseline score based on 12-week data, 1-year results based on 12 + 52 weeks follow-up data)

The results of the Fernandez 2014 study indicate that there is no change in the UPDRS I after 1 year of treatment vs baseline. In Olanov 2014/Slevin 2015, worsening of UPDRS I was found.

In the economic analysis, the weighted average % change after first year of treatment vs baseline was calculated based on data from all studies reporting respective data (Table 58): 4.72%. It was conservatively assumed that UPDRS I score does not change immediately after treatment initiation. Effectiveness after 2 years of treatment was assumed to be the same as after 1 year of treatment. The final model assumptions are presented in Table 59.

Table 59.
CDLCI effectiveness – UPDRS I – CE model assumptions

Parameter	Treatment initiation		Year 1		Year 2		Sources
	Mean	SE	Mean	SE	Mean	SE	
UPDRS I – percentage change from baseline	0.00%	0.00%	4.72%	0.90%	4.72%	0.90%	Fernandez 2014 Olanov 2014/Slevin 2015

UPDRS II

CDLCI effectiveness data on the UPDRS part II scale were reported in 5 studies and data for 5 different time points are available. Data on percentage changes in the UPDRS II vs baseline calculated from these studies are presented in Table 60.

Table 60.
CDLCI effectiveness– UPDRS II – data included in the analysis

Study	Baseline score (no of patients)	Percentage change vs baseline (number of patients)				
		4 weeks	12 weeks	6 months	1 year	2 years
Antonini 2013	14.78 (73)	-	-	-28.1% (53)	-20.0% (43)	-5.7% (33)
Antonini 2014 (GLORIA)	16.50 (172)	-	-	-12.7% (69)	-18.8% (56)	-
Caceres-Redondo 2014	14.50 (16)	-	-	-	-	13.8% (16)

Study	Baseline score (no of patients)	Percentage change vs baseline (number of patients)				
		4 weeks	12 weeks	6 months	1 year	2 years
Fernandez 2014	17.40 (293)	-32.2% (286)	-31.0% (279)	-30.5% (269)	-24.1% (251)	-
Olanov 2014 / Slevin 2015[a]	11.60 (36)	-	15.5% (35)	-	4.3% (33)	-
Olanov 2014 / Slevin 2015[b]	11.80 (33)	-	-	-	-8.5% (26)	-

a) patients randomized to CDLCI at baseline who continued CDLCI treatment for 12 + 52 weeks (baseline score based on baseline data, 12 + 52 weeks follow-up data used as proxy for 1 year results);
b) patients randomized to BMT at baseline who started CDLCI after 12 weeks and continued CDLCI for further 52 weeks (baseline score based on 12-week data, 1-year results based on 12 + 52 weeks follow-up data)

Results of 3 studies reporting data for more than one time point indicate that CDLCI treatment positively affects UPDRS II score, however the effect diminishes over time (Antonini 2013, Fernandez 2014, Olanov 2014 / Slevin 2015). On the other hand, results from Antonini 2014 indicate that CDLCI effectiveness after 1 year of treatment is higher than after 6 months of treatment. Two data sets reporting results at single time points – Caceres-Redondo 2014, Olanov 2014 / Slevin 2015 (in group of patients randomised to CDLCI at baseline) – show deterioration in activities of daily living aspects after 2 years and 1 year of CDLCI treatment, respectively.

For the purposes of CE model, the effectiveness was estimated as follows:

1. The weighted average % change after 1 year of treatment vs baseline (the most commonly considered time point in studies included in the analysis) was calculated based on the results of 4 studies (5 groups of patients) reporting respective data – -19.68%.
2. The Fernandez 2014 study results were used to calculate % change at 1 year of treatment relative to initial results – 11.86% worsening after 1 year when compared to initial results (details in Table 61):

Table 61.
CDLCI effectiveness – UPDRS II – relative effectiveness (treatment initiation vs 1 year) data

Study	Parameter	Baseline (no of patients)	Treatment initiation (no of patients)	1 year (no of patients)
Fernandez 2014	**Mean value**	17.40 (293)	11.80 (286)	13.20 (251)
	% change	-	-	11.86% (vs initial)

The estimated average % change after 1 year of treatment vs baseline (-19.68%) and % change at 1 year of treatment relative to initial results (11.86% worsening) were combined to calculate % change at treatment initiation vs baseline – -28.20% [(1 – 19.68%) / (1 + 11.86%) – 1].

3. The Antonini 2013 study results were used to calculate % change at 2 years of treatment relative to year 1 – 17.92% worsening after 2 years when compared to year 1 results (details in Table 62):

Table 62.
CDLCI effectiveness – UPDRS II – relative effectiveness (1 year vs 2 years) data

Study	Parameter	Baseline	1 year	2 years
Antonini 2013	**Mean value**	14.78 (73)	11.83 (43)	13.95 (33)
	% change	-	-	17.92% (vs 1 year)

The estimated average % change after 1 year of treatment vs baseline (-19.68%) and % change at 2 years of treatment relative to year 1 (17.92% worsening) were combined to calculate % change after 2 years of treatment vs baseline – -5.29% [(1 – 19.68%) x (1 + 17.92%) – 1].

The final model assumptions are presented in Table 63.

Table 63.
CDLCI effectiveness – UPDRS II – CE model assumptions

Parameter	Treatment initiation		Year 1		Year 2		Sources
	Mean	SE	Mean	SE	Mean	SE	
UPDRS II – percentage change from baseline	-28.20%	0.17%	-19.68%	0.52%	-5.29%	2.13%	Antonini 2013 Antonini 2014 (GLORIA) Fernandez 2014 Olanov 2014 / Slevin 2015

UPDRS III

CDLCI effectiveness data on the UPDRS part III scale were reported in 10 studies (11 publications). In 5 studies, CDLCI effectiveness was assessed at a single time point only. Data on percentage changes in the UPDRS III vs baseline calculated from all studies included in the analysis are presented in Table 64.

Table 64.
CDLCI effectiveness in clinical studies – UPDRS III – data included in the analysis

Study	Baseline score (no of patients)	Percentage change (number of patients)				
		4 weeks	12 weeks	6 months	1 year	2 years
Antonini 2008	24.60 (22)	-	-	-	-3.3% (22)	0.8% (22)
Antonini 2013	25.34 (73)	-	-	-10.9% (55)	-7.9% (47)	6.7% (29)
Antonini 2014 (GLORIA)	26.50 (172)	-	-	-11.3% (87)	-12.5% (74)	-
Caceres-Redondo 2014	27.20 (16)	-	-	-	-	8.5% (16)
Fernandez 2014	28.80 (291)	-34.0% (286)	-30.6% (279)	-31.6% (269)	-27.8% (251)	-
Honig 2009	19.10 (22)	-	-	-39.3% (22)	-	-
Karlsborg 2010	36.80 (12)	-44.6% (12)	-	-	-	-

Study	Baseline score (no of patients)	Percentage change (number of patients)				
		4 weeks	12 weeks	6 months	1 year	2 years
Olanow 2014 / Slevin 2015[a]	18.10 (36)	-	-8.3% (35)	-	8.3% (33)	-
Olanow 2014 / Slevin 2015[b]	22.50 (33)	-	-	-	-2.2% (25)	-
Palhagen 2012	24.40 (27)	-	-	-	-11.9% (25)	-
Sensi 2014	35.50 (17)	-	-	-5.9% (17)	-	-

a) patients randomized to CDLCI at baseline who continued CDLCI treatment for 12 + 52 weeks (baseline score based on baseline data, 12 + 52 weeks follow-up data used as proxy for 1 year results);
b) patients randomized to BMT at baseline who started CDLCI after 12 weeks and continued CDLCI for further 52 weeks (baseline score based on 12-week data, 1-year results based on 12 + 52 weeks follow-up data)

All studies indicate an improvement in UPDRS III after CDLCI initiation (based on 4-week, 12-week and 6-month data). However, results of 3 studies (Antonini 2008, Antonini 2013, Caceres-Redondo 2014, Olanow 2014/Slevin 2015) showed worsening (in relation to baseline values) at further time points (1 year, 2 years), indicating that this effect diminishes over time. This is consistent with results of Zibetti 2013 [50] study (excluded from final calculations as data presented after mean follow-up).

For the purposes of CE model, the effectiveness was estimated as follows:

1. The weighted average % change after 1 year of treatment vs baseline (the most commonly considered time point in studies included in the analysis) was calculated based on the results of 6 studies (7 groups of patients) reporting respective data – -17.65%.
2. The Fernandez 2014 study results were used to calculate % change at 1 year of treatment relative to initial results (4 weeks results) – 9.47% worsening after 1 year when compared to initial results (details in Table 65):

Table 65.
CDLCI effectiveness – UPDRS III – relative effectiveness (treatment initiation vs 1 year) data

Study	Parameter	Baseline	Treatment initiation	1 year
Fernandez 2014	**Mean value**	28.80 (291)	19.00 (286)	20.80 (251)
	% change	-	-	9.47% (vs initial)

The estimated average % change after 1 year of treatment vs baseline (-17.65%) and % change at 1 year of treatment relative to initial results (9.47% worsening) were combined to calculate % change at treatment initiation vs baseline – -24.77% [(1 - 17.65%) / (1 + 9.47%) – 1].

3. The Antonini 2008 and Antonini 2013 study results were used to calculate % change at 2 years of treatment relative to year 1 – 17.92% worsening after 2 years when compared to year 1 results (weighted average, details in Table 66):

Table 66.
CDLCI effectiveness – UPDRS III – relative effectiveness (1 year vs 2 years) data

Study	Parameter	Baseline	1 year	2 years
Antonini 2008	**Mean value**	24.60(22)	23.80 (22)	24.80 (22)
	% change	-	-	4.20% (vs 1 year)
Antonini 2013	**Mean value**	25.34 (73)	23.33 (47)	27.05 (29)
	% change	-	-	15.95% (vs 1 year)
Weighted average % change [a]			-	10.88% (vs 1 year)

a) weighted with number of patients at 2 years

The estimated average % change after 1 year of treatment vs baseline (-17.65%) and % change at 2 years of treatment relative to year 1 (10.88% worsening) were combined to calculate % change after 2 years of treatment vs baseline – -8.69% [(1 – 17.65%) x (1 + 10.88%) – 1].

The final model assumptions are presented in Table 67.

Table 67.
CDLCI effectiveness – UPDRS III – CE model assumptions

Parameter	Treatment initiation		Year 1		Year 2		Sources
	Mean	SE	Mean	SE	Mean	SE	
UPDRS III – percentage change from baseline	-24.77%	0.21%	-17.65%	0.62%	-8.69%	3.55%	Antonini 2008 Antonini 2013 Antonini 2014 (GLORIA) Fernandez 2014 Honig 2009 Olanow 2014 / Slevin 2015 Palhagen 2012

UPDRS IV

CDLCI effectiveness data on the UPDRS part IV scale were reported in 6 studies and data for 3 time points are available. Data on percentage changes in the UPDRS IV vs baseline calculated from these studies are presented in Table 68.

Table 68.
CDLCI effectiveness– UPDRS IV – data included in the analysis

Study	Baseline score (no of patients)	Percentage change (no of patients)		
		6 months	1 year	2 years
Antonini 2008	8.40 (22)	-	-23.8% (22)	-21.4% (22)
Caceres-Redondo 2014	8.70 (16)	-	-	-23.0% (16)
Honig 2009	10.50 (22)	-57.1% (22)	-	-
Martinez-Martin 2014	9.93 (44)	-56.1% (44)	-	-
Palhagen 2012	9.40 (27)	-	-39.4% (25)	-

Study	Baseline score (no of patients)	Percentage change (no of patients)		
		6 months	1 year	2 years
Sensi 2014	8.40 (17)	-33.3% (17)	-	-

All studies indicate an improvement in part IV of UPDRS. For the purposes of CE model, the effectiveness was estimated as follows:

1. The weighted average % change after 1 year of treatment vs baseline was estimated based on studies reporting 1-year outcomes and studies with 6-month outcomes indicating better therapeutic effect than seen at 1 year (Honig 2009, Martinez-Martin 2014) – -44.61%.
2. The Antonini 2008 study results were used to calculate % change at 2 years of treatment relative to year 1 – 3.12% worsening after 2 years when compared to year 1 results (details in Table 69):

Table 69.
CDLCI effectiveness – UPDRS IV – relative effectiveness (1 year vs 2 years) data

Study	Parameter	Baseline (no of patients)	1 year (no of patients)	2 years (no of patients)
Antonini 2008	**Mean value**	8.40 (22)	6.40 (22)	6.60 (22)
	% change	-	-	3.12% (vs 1 year)

The estimated average % change after 1 year of treatment vs baseline (-44.61%) and % change at 2 years of treatment relative to year 1 (3.12% worsening) were combined to calculate % change after 2 years of treatment vs baseline – -42.88% [(1 - 44.61%) x (1 + 3.12%) – 1].

3. It was conservatively assumed that initial % change vs baseline is the same as after first year of treatment (-44.61%).

The final model assumptions are presented in Table 70.

Table 70.
CDLCI effectiveness – UPDRS IV – CE model assumptions

Parameter	Treatment initiation		Year 1		Year 2		Sources
	Mean	SE	Mean	SE	Mean	SE	
UPDRS III – percentage change from baseline	-44.61%	1.29%	-44.61%	1.29%	-42.88%	0.41%	Antonini 2008 Honig 2009 Martinez-Martin 2014 Palhagen 2012 Sensi 2014

B.2. Long-term effectiveness/progression

Long-term UPDRS outcomes were modelled based on data identified in the systematic reviews. (details in Appendix A). For CSAI and CDLCI, no treatment specific long-term UPDRS data were identified. The analyses of BMT and DBS data are described in sections B.2.1 and B.2.2. Final model assumptions are presented in section B.2.3.

B.2.1. UPDRS "natural disease progression" – data from "BMT studies"

Results of studies identified in the systematic review (details in section A.3) and included in the analysis are summarised in the table below. Study results were used to calculate a UPDRS change (points change) per year.

Data on UPDRS IV progression were not identified. In some studies data on time to occurrence of motor complications or dyskinesia are shown based on Kaplan-Meier curves. In Hely 2005 [265] study additional data on ON/OFF periods occurrence are presented, including its severity. In economic analysis by Palmer 2002 [317] also a half-year probability for ON/OFF intensification increase were used. However, all these data are not sufficient to estimate change in total part IV of UPDRS over time. Therefore, data from EARLYSTIM (BMT arm) were also considered for estimation of UPDRS IV progression in the model, and for the analysis to derive UPDRS I-III progression rates (see Table 71).

Table 71.
Long-term UPDRS progression in BMT studies – data used in the analysis

Study	UPDRS change [points per year]				Note
	I	II	III	IV	
Alves 2005	-	1.900	3.300	-	General PD group; data reported directly in publication
Brooks 2008	-	-	1.000	-	Patients from clinical study treated with entacapone; data reported directly within study; value refers to period when initial improvement run out
Jankovic 2001	0.167	0.560	0.704	-	General PD group; data reported directly in publication
LeWitt 2013	-	1.799	1.967	-	Patients from clinical studies treated with levodopa or rotigotine; baseline value (since disease starts to progress) and at the end of follow-up taken from graph; annual change for 2 groups calculated and then averaged
Reinosso 2014	-	-	2.120	-	Data from period 7-9 years after treatment initiation; data reported directly in publication
Schrag 2000	-	-	0.378	-	Data from clinic based group with Hoehn&Yahr score 3-5; in study percentage change was reported (0.35%) and here is transformed into point change (0.35% x 108 [UPDRS III range])
EARLYSTIM BMT arm	0.235	0.300	0.650	0.355	Calculated as difference between baseline and 2-year value divided by follow-up period [2 years]
Mean*	**0.201**	**1.136**	**1.447**	**0.355**	

* not weighted mean as number of patients in the studies not always reported.

B.2.2. UPDRS long-term progression in DBS studies

Data on UPDRS long-term outcomes were also collected from DBS studies, in the systematic review described in section A.2. Only studies reporting UPDRS scores at least at two follow-up time-points with first of them at least 2 year after treatment initiation were included in the analysis (other selection criteria listed in section A.2.2). Data used in the analysis are summarised in Table 72, Table 73, Table 74, Table 75. In order to avoid using the same patient group data more than once, publications were collected into groups describing the same data and considered as one study.

Table 72.
DBS long-term effectiveness - UPDRS I – data used in the analysis

Study	Mean UPDRS I (no of patients)						
	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	10 yrs.
Gan 2007 / Gervais-Bernard 2009		2.40 (36)		2.57 (23)			
Hung 2013	2.90 (60)			3.30 (31)		3.80 (17)	
Kim 2013	2.90 (52)	3.20 (52)	3.60 (<52) [a]	4.40 (<52) [a]	4.50 (<52) [a]	3.00 (<52) [a]	
Kishore 2010		1.20 (36)		2.10 (29)			
Weaver 2012	2.88 (157)	3.23 (159)					
Schupbach 2005	2.00 (32)			3.30 (30)			
Janssen 2014				3.10 (18)			4.20 (12)
Wider 2008	2.60 (36)			3.70 (37)			

a) exact number of patients not reported (for the purposes of the analysis 52 assumed at all time points)

Table 73.
DBS long-term effectiveness - UPDRS II (on med / on stim) – data used in the analysis

Study	Mean UPDRS II (no of patients)							
	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	10 yrs.
Aviles-Olmos 2014				13.20 (41)			15.20 (12)	
Gan 2007 / Gervais-Bernard 2009		10.40 (36)	11.35 (23)					
Krack 2003		10.70 (40)		14.00 (39)				
Kim 2013	10.30 (52)	10.70 (52)	11.10 (<52) [a]	12.50 (<52) [a]	12.80 (<52) [a]	12.70 (<52) [a]		
Kishore 2010		7.30 (36)		7.10 (29)				
Li 2013				10.90 (31)			16.70 (29)	
Weaver 2012	14.97 (155)	17.50 (157)						
Piboolnurak 2007		13.20 (33)		14.60 (17)				
Romito 2009		8.90 (20)		8.60 (20)				
Schupbach 2005	10.00 (32)			14.30 (30)				
Janssen 2014				14.30 (18)				20.40 (12)

Study	Mean UPDRS II (no of patients)							
	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	10 yrs.
Wider 2008	12.80 (36)			18.90 (37)				

a) exact number of patients not reported (for the purposes of the analysis 52 assumed at all time points)

Table 74.
DBS long-term effectiveness - UPDRS III (on med / on stim) – data used in the analysis

Study	Mean UPDRS III (no of patients)							
	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	10 yrs.
Aviles-Olmos 2014				23.90 (41)			28.70 (12)	
Fasano 2010		22.90 (20)		21.40 (20)			26.90 (20)	
Gan 2007 / Gervais-Bernard 2009		12.50 (36)		13.17 (23)				
Krack 2003		15.30 (40)		21.10 (39)				
Kim 2013	17.70 (52)	18.50 (52)	18.50 (<52) [a]	22.10 (<52) [a]	21.80 (<52) [a]	22.10 (<52) [a]		
Kishore 2010		14.70 (36)		16.50 (29)				
Weaver 2012	19.43 (146)	21.96 (143)						
Paek 2013	14.20 (41)	19.50 (41)						
Piboolnurak 2007		23.00 (33)		24.80 (17)				
Schupbach 2005	10.10 (32)			17.90 (30)				
Janssen 2014				21.70 (18)				28.70 (12)
Toft 2011	15.40 (110)	18.10 (89)	19.50 (52)	22.40 (32)				
Wider / Aybek 2007	27.70 (36)	25.10 (43)		30.60 (37)				

a) exact number of patients not reported (for the purposes of the analysis 52 assumed at all time points)

Table 75.
DBS long-term effectiveness - UPDRS IV – data used in the analysis

Study	Mean UPDRS IV (no of patients)						
	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	10 yrs.
Gan 2007 / Gervais-Bernard 2009		3.10 (36)		3.26 (23)			
Hung 2013	1.80 (60)			1.90 (31)		1.80 (17)	
Kim 2013	4.40 (52)	4.60 (52)	4.80 (<52) [a]	6.00 (<52) [a]	6.40 (<52) [a]	5.40 (<52) [a]	
Merola 2014		2.72 (174)		3.32 (174)			
Weaver 2012	4.56 (122)	4.21 (124)					
Schupbach 2005	3.20 (32)			5.10 (30)			
Janssen 2014				2.40 (18)			2.30 (12)

a) exact number of patients not reported (for the purposes of the analysis 52 assumed at all time points)

The data presented in the tables above were furtherly analyzed with use of linear regression (geeglm function from geepack package for R version 3.2.2) to derive long-term progression rates in patients treated with DBS (separately for each UPDRS score). Use of geeglm function allowed for estimation of single annual progression rate for each UPDRS score based on data from different groups of patients reported at multiple time points (not necessarily the same time points in all groups of patients), weighted with number of patients in each group that was changing over time (patients were lost to follow-up).

Table 76 shows calculations results for UPDRS long-term progression. The estimated mean annual progression rate for each UPDRS scores together with SE are presented. Additionally, statistical significance of results can be assessed based on p-value estimated. Assuming significance level of 0.005, it can be concluded that results for all UPDRS scores are statistically significant (p-value < 0.005), indicating that all UPDRS scores do not remain constant in the long-term setting.

Table 76.
Long-term UPDRS progression – results from regression analyses in DBS studies

Parameter	Annual rate of progression		
	Mean	Standard Error	p-value
UPDRS I	0.19301	0.02267	<0.005
UPDRS II	0.940	0.229	<0.005
UPDRS III	1.366	0.214	<0.005
UPDRS IV	0.2685	0.0551	<0.005

The reliability of the results presented above is limited. In most of the studies availability of the UPDRS data decreased with increasing follow-up – patients were lost to follow-up for various reasons and results at further time points were based on data with low number of patients. Consequently, UPDRS changes would possibly differ from those assumed in the analysis, if only results for patients with longer follow-up were taken into account also in earlier time points. However, given data availability, it was not possible to take into account the impact of withdrawals on reported changes in UPDRS scores.

Moreover, in none of the studies listed in above tables, statistical analysis of the changes in UPDRS scores over time was performed, except Schupbach 2005. The results reported in the Schupbach 2005 study (data presented in Table 75) suggest that UPDRS IV score after 5 years of treatment is almost 2 points worse than after 2 years (5.10 at year 5 vs 3.20 at year 2). However, in this analysis, the observed worsening in UPDRS IV was not statistically significant and so the results do not allow a rejection of the hypothesis that UPDRS IV remains constant in the long term setting.

B.2.3. CE model assumptions

Results of the analysis of long-term UPDRS progression in DBS and BMT studies are summarized in Table 77. The table contains also results of Krack 2003 study [128], one of the DBS studies included in the analysis, deemed to be representative for UPDRS III progression in population under consideration, based on clinical expert opinion. As mentioned before, long term evidence for CSAI and CDLCI was not identified.

Given the data availability, reliable assessment of possible changes in progression rates over time (depending on duration of disease, treatment, motor complication etc.) was not possible. Thus, long term UPDRS progression is expressed in terms of a constant annual progression rates.

Table 77.
Long-term UPDRS progression – results of the analysis

Source	Annual progression rate							
	UPDRS I		UPDRS II		UPDRS III		UPDRS IV	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
BMT studies	0.201	0.020	1.136	0.114	1.447	0.145	0.355 [b]	0.223 [b]
DBS studies	0.193	0.023	0.940	0.229	1.366	0.214	0.269	0.055
Krack 2003 [a]			1.650 [c]	0.335	2.425 [c]	0.595		

a) One of the DBS studies deemed to be representative for UPDRS III progression in population under consideration (clinical expert opinion)
b) Based solely on EARLYSTIM results (BMT arm)
c) Based on 1-year and 5-year follow-up data (see Table 30 and Table 31)

Based on clinical expert opinion, it was assumed that long term progression rates are the same, irrespective of treatment used (DBS, BMT, CSAI, CDLCI). Assumed progression rates (details below) are applied in the model from year 3 onwards, with the exception of UPDRS IV in DBS, CSAI and CDLCI patients. For UPDRS IV, the value from the EARLYSTIM trial (DBS arm) at year 2 is held constant (no progression) for a further 8 years in the DBS arm, and the same progression rate as for the BMT arm is applied thereafter. The basis for this assumption was expert opinion indicating that the main impact of DBS in reducing complications of therapy is maintained in the long-term. The same assumption (UPDRS IV at year 2 held constant for a further 8 years) was applied for CSAI and CDLCI.

The following data sources were used in base case analysis:

- data from BMT studies for UPDRS I & II (for all treatments arms from year 3 onwards),
- data from Krack 2003 [128] for UPDRS III (for all treatments arms from year 3 onwards) – assumption based on expert opinion,
- data from EARLYSTIM trial (BMT arm) for UPDRS IV (from year 3 onwards for the BMT arm, from year 11 onwards for the DBS, CSAI and CDLCI arms).

Due to high uncertainty in estimated progression rates alternative data sources were considered in the sensitivity analysis. Assumptions of base case scenario and sensitivity analysis scenarios are presented in Table 78.

Table 78
Long-term UPDRS progression – model input data

Parameter	UPDRS I		UPDRS II		UPDRS III		UPDRS IV	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Base case scenario								
Annual progression rate	**0.201**	**0.020**	**1.136**	**0.114**	**2.425**	**0.595**	**0.355**	**0.223**
Source	**BMT studies**		**BMT studies**		**Krack 2003**		**EARLYSTIM**	
Sensitivity analysis – scenario 1								
Annual progression rate	0.201	0.020	1.650	0.335	2.425	0.595	0.355	0.223
Source	BMT studies		Krack 2003		Krack 2003		EARLYSTIM	
Sensitivity analysis – scenario 2								
Annual progression rate	0.193	0.023	0.940	0.229	1.366	0.214	0.355	0.223
Source	DBS studies		DBS studies		DBS studies		EARLYSTIM	
Sensitivity analysis – scenario 3								
Annual progression rate	0.201	0.020	1.136	0.114	1.447	0.145	0.355	0.223
Source	BMT studies		BMT studies		BMT studies		EARLYSTIM	
Sensitivity analysis – scenario 4								
Annual progression rate	0.201	0.020	1.136	0.114	2.425	0.595	0.178	-
Source	BMT studies		BMT studies		Krack 2003		2-fold deceleration of progression in relation to EARLYSTIM data	
Sensitivity analysis – scenario 5								
Annual progression rate	0.201	0.020	1.136	0.114	2.425	0.595	0.710	-
Source	BMT studies		BMT studies		Krack 2003		2-fold acceleration of progression in relation to EARLYSTIM data	

Assumptions that were changed in sensitivity analysis (as compared to base case scenario) underlined

Additionally, scenarios assuming different response duration for DBS, CSAI and CDLCI were explored in the sensitivity analysis:

- for UPDRS I-III: value at year 2 held constant (no progression) for a further 2 years, and the same progression rate as for BMT arm applied thereafter;
- for UPDRS IV: the same progression rate as for BMT arm applied from year 3 onwards.

B.3. Adverse events

Data on adverse events associated with DBS, CSAI and CDLCI were identified in the systematic review (details in Appendix A).

Due to high heterogeneity in reporting of adverse events in DBS studies identified in the systematic review, based on their results it was not possible to reliably estimate frequency of adverse events that influence patient's quality of life or generate costs (and thus are worth considering in the model). Data

on adverse events in the EARLYSTIM study (both published and unpublished patient-level data) were used to estimate relevant inputs for the model, for both DBS and BMT. Detailed information on EARLYSTIM-based adverse event analysis is provided in section **Error! Reference source not found.**.

The following sections present data on skin nodules frequency in CSAI studies (section B.3.1) and peritonitis frequency in CDLCI studies (section B.3.2), included from the studies identified in the systematic review.

B.3.1. CSAI – skin nodules frequency

Studies reporting data on skin nodules / skin reaction frequency during CSAI treatment were identified in systematic review (details in section A.1). The data from studies included in the analysis are presented in Table 79. Based on these data weighted mean frequency of skin nodules/ skin reaction occurrence was calculated (74.56%). Given the lack of long term data, this rate was applied only within the 1st year of treatment.

Table 79.
Adverse event (skin nodules / skin reaction) in clinical trials – CSAI treatment

Study	Number of patients	Patients with events	% with events	Note
Antonini 2011 / de Gaspari 2006	12	2	17%	Based on Antonini 2011
Drapier 2012	23	23	100%	-
Elia 2012	10	5	50%	-
Garcia-Ruiz 2008	82	56	68%	In 7 patients with severe grade
Hughes 1993 / Frankel 1990	25	25	100%	Based on Frankel 1990
Katzenschlager 2005	12	9	75%	-
Morgante 2004 / di Rosa 2003	10	10	100%	Based on Morgante 2004
Pietz 1998	25	25	100%	-
Poewe 1993	18	4	22%	-
Stibe 1988	11	11	100%	-
Total	228	170	**74.56%**	
SE			**2.88%**	

Additionally in Stocchi 1993 , Stocchi 2001 and Manson 2002 skin nodules / skin reaction occurred in almost all patients but no detailed data were presented

B.3.2. CDLCI – peritonitis frequency

Due to the heterogeneity in reporting of adverse events in studies identified in the systematic review, the device related AEs rates were estimated based on Nyholm 2008 [45] as this study was also used in other economic analyses (Lowin 2011, Walter 2014 [318, 319]).

Data on peritonitis frequency during CDLCI treatment were retrieved from the studies identified in the systematic review, and the analysis of the data is presented in Table 80. Based on these data, a weighted mean frequency of peritonitis occurrence was calculated (3.23%). Given the lack of long term data, this rate was applied only within the 1st year of treatment.

Table 80.
Occurrence of peritonitis during CDLCI treatment – data from clinical studies

Study	Number of patients	Peritonitis	
		Number of events	Probability of event
Antonini 2013d	98	4	4.08%
Devos 2009	91	4	4.40%
Fernandez 2014	324	9	2.78%
Martinez-Martin 2014	44	1	2.27%
Palhagan 2012	37	1	2.70%
Sensi 2014	28	2	7.14%
Zibetti 2014	59	1	1.69%
Total	681	22	3.23%
SE			0.03%

B.4. Withdrawal

Data on withdrawal rates for CSAI and CDLCI were sourced from studies identified in the systematic review of CSAI and CDLCI efficacy (details in section A.1).

B.4.1. CSAI

Detailed data on treatment discontinuation (including information on follow-up period) were available in 9 studies (12 publications). Data on withdrawal rates in the studies included in the analysis are presented in Table 81. Only withdrawals due to adverse events, lack of efficacy or due to own patient decision were included in the calculations.

Table 81.
Discontinuation of CSAI treatment – data included in the analysis

Study	Total number of patients	Discontinuation		Follow-up [years]	Reasons for withdrawal
		Number of patients	% of patients		
Antonini 2011 / de Gaspari 2006	12	6	50.0%	5.00 / 2.50 [a / b]	AEs or no effectiveness (6)
Drapier 2012	23	0	0.0%	1.00 [a]	-
Hughes 1993 / Frankel 1990	25	6	24.0%	3.04 [b]	AEs (4), other (2)

Study	Total number of patients	Discontinuation		Follow-up [years]	Reasons for withdrawal
		Number of patients	% of patients		
Katzenschlager 2005	12	0	0.0%	0.50 [a]	-
Manson 2002	64	8	12.5%	2.82 [b]	AEs (3), patient's decision (2), unable to continue (3)
Martinez-Martin 2014	43	0	0.0%	0.50 [a]	-
Morgante 2004 / di Rosa 2003	12	1	8.3%	2.00 [a]	infection (1)
Poewe 1993	18	4	22.2%	1.72 [b]	AEs (3), no effectiveness (1)
Todorova 2013	20	5	25.0%	2.00 [a]	skin reaction (5)

a) total follow-up of the study; b) mean follow-up

The probability of treatment discontinuation was calculated based on data from all studies listed above. In the first step, yearly probability of discontinuation was calculated for each study (probability from de Gaspari 2006 was calculated based on mean follow-up period, data on total follow-up period was not used), assuming constant yearly withdrawal. In the second step, the weighted mean withdrawal probability was estimated for all studies. Values of weights were assumed to be equal to the product of number of patients and follow-up period in each study. A summary of calculations is presented in Table 82. The weighted mean was 7.59% (SD 0.12%) and this value was used in the model.

Table 82.
Discontinuation of CSAI treatment – model input data

Study	Annual discontinuation probability	Weight
Antonini 2011 / de Gaspari 2006	12.94%	30.00
Drapier 2012	0.00%	23.00
Hughes 1993 / Frankel 1990	8.63%	76.04
Katzenschlager 2005	0.00%	6.00
Manson 2002	4.63%	180.27
Martinez-Martin 2014	0.00%	21.50
Morgante 2004 / di Rosa 2003	4.26%	24.00
Poewe 1993	13.62%	30.90
Todorova 2013	13.40%	40.00
Mean	**7.59%**	-
SD	**0.12%**	-

B.4.2. CDLCI

Detailed data on treatment discontinuation were available in 6 studies. Moreover, one study – Nyholm 2012 [320] – was identified in non-systematic search. Detailed data sourced from all included studies are presented in Table 83. Discontinuation rates were estimated separately for initial phase / test phase of treatment, first year of treatment (initial phase excluded) and subsequent years of treatment, according to the information in the studies.

Table 83.
Discontinuation of CDLCI treatment – data included in the analysis

Study	Total number of patients	Discontinuation		Note
		Number of patients	% of patients	
Test phase / initial treatment period				
Antonini 2014 (GLORIA)	172	8	8.5%	**Test phase:** run-in period (approximately 7-14 days period for verification of effectiveness and dose) – CDLCI infusion via nasoduodenal tube **Discontinuation reason:** not reported in details
Fernandez 2014	354	22[a]	6.2%	**Test phase:** nasojejunal (NJ) titration period (2-14 days) and a PEG-J titration period (2-14 days) **Discontinuation reason:** withdrew consent (12), AEs (5), lack of efficacy (5)
Nyholm 2008	58	7	12.1%	**Test phase:** nasodoudenal test period for an average 12 days (range: 3-30) **Discontinuation reason:** not reported in details
Palhagen 2012	37	10	27.0%	**Test phase:** initiation nasoduodenal CDLCI + period before permanent CDLCI implantation (3 months) **Discontinuation reason:** withdrew consent (3), AEs (2), lack of efficacy (5)
1st year of treatment				
Eggert 2008	13	4	30.8%	**Discontinuation reason:** patient's refusing (1), AEs (1), mechanical and physical problems (2)
Fernandez 2014	324	37[b]	16.0%	**Discontinuation reason:** withdrew consent (13), AEs (22), lack of efficacy (2)
Slevin 2005	29	5	17.2%	**Discontinuation reason:** withdrew consent (13), AEs (22), lack of efficacy (2)
Subsequent years				
Nyholm 2012	135	31	23.0%[c]	**Discontinuation reason:** AEs or lack of effectiveness **Time period:** mean follow-up 4.2 years; restricted mean treatment time estimated with Kaplan–Meier methodology (censoring at the end of the study or death): 7.79 years

a) additional 8 patients withdrew due to administrative reason or protocol violation. According to methodology not included in calculation
b) additional 15 patients withdrew due to administrative reason or protocol violation. According to methodology not included in calculation
c) cumulative discontinuation rate for the whole follow-up period

In the Palhagen 2012 study, discontinuation rate reported for test phase in much higher than in other studies. This might be caused by fact that longer period was considered in this trial (3 months vs up to 1 month in other trials). So in the final calculations data from Palhagen 2012 were not included. Discontinuation rate in initial treatment period was calculated based on the results reported in Antonini

2014 (GLORIA), Fernandez 2014 and Nyholm 2008 – 6.34%. In the model it was assumed that only costs of trial tube insertion and removal are borne in patients who discontinue treatment in initial/test period. The effectiveness of treatment was not considered in such cases – it was assumed that treatment in test period has no effect on UPDRS scores (modelling of UPDRS scores is the same as in patients treated continuously with BMT).

The percentage of patients who stop treatment after treatment initiation but still within the first year of treatment was calculated based on data from all 3 studies identified – Eggert 2008, Fernandez 2014, Slevin 2005 – 12.57%.

Probability of treatment discontinuation in subsequent years was calculated based on Nyholm 2012. Cumulative discontinuation rate for the whole follow-up period (23.0% in 7.79 years) was rescaled to calculate annual discontinuation rate (assumed to be constant over time) – 3.29%.

Summary of discontinuation rates applied in the model is provided in Table 84.

Table 84
Discontinuation of CDLCI treatment – model input data

Treatment period	Discontinuation probability	
	Mean	SD
Test phase / initial period	6.34%	0.17%
1st year	12.57%	0.25%
Year 2 and every year thereafter	3.29%	0.13%

B.5. CSAI dose

Studies reporting data on CSAI dose were identified in the systematic review of CSAI efficacy (details in section A.1). Studies with dose presented as mean daily dose reported were included, whereas studies reporting data on dose as median, as dose per hour or in some specified subgroups of patients were excluded. Finally, 12 studies (described in 15 publications) were included in the analysis.

Mean daily dose of CSAI was calculated using data on mean dose after achieving optimal dosage or mean dose within study follow-up. In case data was available at several time points in the study, data from the last time point were used. This assumption has no effect on the results of the analysis as the differences in daily doses over time were not significant in such cases.

Detailed data from single studies used in calculation are presented below, together with mean daily dose weighted by number of patients.

Table 85.
Daily doses of CSAI in clinical studies

Study	Number of patients	Dose per day [mg]		Note
		Mean	SD	
Antonini 2011 / de Gaspari 2006	12	83.40	19.20	-
Drapier 2012	23	62.60	18.80	-
Garcia-Ruiz 2008	82	72.00	21.38	-
Hughes 1993 / Frankel 1990	22	80.80	31.60[a]	data from Hughes 1993 taken; mean dose after initial stabilization
Katzenschlager 2005	8	84.70	33.13[a]	data form UK patients group
Manson 2002	45	102.50	71.80	data from monotherapy group
Martinez-Martin 2014	43	105.90	23.20	-
Morgante 2004 / di Rosa 2003	12	100.00	39.11[a]	-
Poewe 1993	14	160.00	62.58[a]	data from patients with complete follow-up
Stibe 1988	11	77.00	30.12[a]	-
Stocchi 2001	30	51.60	34.80	-
Todorova 2013	20	105.30	23.90	-
Weighted average		**86.67**	**2.45**	

a) SD value not reported within the study; calculated based on relation of SD to mean from other studies (39.11%)

B.6. Falls

No separate systematic review was performed to identify data on falls in PD patients. Relevant data were selected from studies identified in the search for progression data in BMT studies (details in section A.3). Initial selection was based on titles and abstracts and only studies specifically aimed at assessing falls in PD patients were included in full text analysis. Out of 15 publications included in full text analysis, 7 were finally included in the analysis (excluded studies did not provide any data relevant for the analysis). Additionally, references from identified publications were analysed and non-systematic search via Google was performed. This allowed to identify another 9 studies.

Altogether, we found 16 studies reporting the % of falls among included PD patients. A brief characteristics of the studies is provided in Table 86 and data extracted from the studies – in Table 87.

Table 86.
Characteristics of studies included in falls data analysis

Study	Study design	Follow-up	No of patients	Age [mean]	Duration of PD [years]	Hoehn & Yahr	UPDRS III
Ashburn 2001	**Design:** prospective **Aim:** To identify one or more features, which would predict individuals at risk of falling during follow-up **Country:** UK	3 months	57	71 (46-86)	not reported	not reported	not reported
Bloem 2001	**Design:** prospective **Aim:** To study the epidemiology, clinical impact and prediction of falls in moderately affected PD patients **Country:** The Netherlands	6 months	59 with PD 55 control	60.8 (9.7)	7.1 (4.8)	2.3 (0.7)	31.5 (11.0)
Cheng 2014	**Design:** prospective **Aim:** To analyze the clinical features, imaging findings, scientific clinical scores, and measurements to determine potential risk factors associated with fall-related fracture in PD **Country:** Taiwan	18 months	100	68.6 (10.6)	5.06 (4.1)	2.7 (1.3)	34.96 (18.31)
Contreras 2012	**Design:** retrospective **Aim:** To determine the relevant risk factors for falling in PD **Country:** Spain	not reported	160	72.0 (9.5)	8.1 (6.4)	2.6 (1.0)	28.8 (15.6)
Gazibara 2014	**Design:** not reported **Aim:** To estimate fall frequency as well as demographic and clinical related factors **Country:** Serbia	6 months	180 fallers 120 non-fallers	62 median for fallers 60 median for non-fallers	7 for fallers 4 for non-fallers	2.5 – fallers 2 – non-fallers	45 – fallers 38 – non-fallers
Johnson 2014	**Design:** prospective **Aim:** To determine the efficacy of clinical tests, balance scales, and stable-platform posturography in detecting postural instability and discriminating between fallers and non-fallers **Country:** Australia	24 months	48	65 (8)	6	2.5 (0.9)	15.3
Kataoka 2011	**Design:** prospective **Aim:** To evaluate factors responsible for falling in PD patients at H&Y III stage **Country:** Japan	6 months	30	68.3 (7.0)	7.12 (5.78)	3 – all patients	19.3 (8.7)
Kerr 2010	**Design:** prospective **Aim:** To determine an optimal combination of functional and disease-specific tests to predict falls in individuals with PD **Country:** Australia	6 months	101	66.4 (8.2)	6.1 (4.4)	2.1 (0.8)	18.7 (9.2)

Study	Study design	Follow-up	No of patients	Age [mean]	Duration of PD [years]	Hoehn & Yahr	UPDRS III
Latt 2009	**Design:** not reported **Aim:** to devise a fall risk screen for people with PD using routine clinical measures and an explanatory (physiological) fall risk assessment for guiding fall prevention interventions **Country:** Australia	12 months	113	66.1	not reported	2.02	not reported
Lindholm 2015	**Design:** prospective **Aim:** To determine factors associated with future falls and/or near falls in people with mild PD. **Country:** Norway	6 months	141	68	2 - median	2 - median	13 - median
Matinolli 2011	**Design:** prospective **Aim:** To evaluate the risk factors for recurrent falling and mortality in PD **Country:** Finland	24 months	125	67.9 (10.2)	6.1 (4.1)	2.3 (0.7)	25.0 (11.1)
Parashos 2012	**Design:** prospective **Aim:** explore risk factors for falls in PD utilizing the cross-sectional, baseline data in the NPF-QII database **Country:** USA	3 months	2,876	68.1 (8.6)	7.6 (5.8)	2.41	not reported
Rudzinska 2013	**Design:** prospective **Aim:** To assess the incidence and risk factors of falls in comparison to a control group **Country:** Poland	12 months	100	67.2 (9.9)	6.2 (3.4)	2.75 (0.65)	32.2 (13.8)
Voss 2012	**Design:** not reported **Aim:** To define the frequency of falls in early PD and assess potential risk factors for falls in this population **Country:** USA	18 months	431	not reported	< 5 years	not reported	not reported
Wielinski 2005	**Design:** retrospective **Aim:** To ascertain frequency, type, risk factors of falling, and resulting injuries among parkinsonian patients **Country:** USA	24 months	1,092	72.7 - median	7.0 - median	not reported	not reported
Wood 2002	**Design:** prospective **Aim:** To accurately establish the incidence of falls in PD and to investigate predictive risk factors for fallers from baseline data **Country:** UK	6 months	101	75 - median	6 - median	1.84	not reported

Table 87.
Falls frequency – data included in the analysis

Study	Number of patients		% of patients with falls	Time period [months]	Total number of falls	Falls per patient-year
	Total	Fallers				
Ashburn 2001	57	22	39%	3	-	-
Bloem 2001	59	30	51%	6	205	6.95
Cheng 2014	100	56	56%	18	123[b]	0.82
Contreras 2012	160	62	39%	not reported	-	-
Gazibara 2014	300	180	60%	6	-	-
Johnson 2014	48	26	54%	24	-	-
Kataoka 2011	30	15	50%	6	-	-
Kerr 2010	101	48	48%	6	-	-
Latt 2009 [a]	113 (total)	51	45%	12	2,160	19.12
	37 (UPDRS III <10)	11	30%		-	-
	43 (UPDRS III 10-19)	20	47%		-	-
	33 (UPDRS III >19)	20	61%		-	-
Lindholm 2015	141	45	32%	6	158	2.24
Matinolli 2011	125	79	63%	24	3,125	12.50
Parashos 2012	2,876	1,069	37%	3	-	-
Rudzinska 2013	100	54	54%	12	194	1.94
Voss 2012	431	93	22%	18	-	-
Wielinski 2005	1092	597	55%	24	-	-
Wood 2002	101	69	68%	6	585	11.58

a) result with division for total UPDRS also available within study; b) mean number of falls per faller in this study was 2.2 and total number of falls was calculated as 56 fallers multiplied by 2.2 falls

The falls data reported by different studies are not consistent and there is a big difference between low and high values. In order to explain differences between reported frequency of falls, patients characteristics in each study were analysed (Table 86). One possible explanation for difference in estimated percentage of fallers can be due to duration of studies – a higher value can be expected for those with longer study duration as they can cover more subjects in later stages of PD.

The following calculations and assumptions were made to arrive at the values for model analyses:

- We have calculated percentage of fallers within model cycle based on data extracted from all 16 studies, resulting in a mean value of 42.78%. As this value is similar to the value reported by Latt 2009 for UPDRS III 10-19 group – 47%, it was assumed that it can be applied to patients at baseline condition in our model (average baseline UPDRS III value of 12.3). Additionally we assumed that there is only one fall per faller.

- The fraction of injurious falls was assessed based on 3 studies. Calculated mean frequency of injurious falls as a percentage of all falls is 50.9% (Table 88) Injurious falls were assumed to lead to hospitalisations.

Table 88.
Frequency of injurious falls – data included in the analysis

Study	No of falls	% of injurious falls
Rudzinska 2013	194	40%
Bloem 2001	150	62%
Contreras 2012	62	58%
Average	**-**	**50.88%**

- The reviewed literature indicates that individual UPDRS I-IV scales as well as total UPDRS values are good predictors of the increase of falls frequency with PD progression [251, 259, 321, 322]. Most data were published for UPDRS III, so this scale was chosen as a predictive factor of PD progression related falls. From the list of reviewed papers, 3 publications containing changes of frequency of falls odds ratio per unit of UPDRS III score increase with data have been selected to extract information used in our model. The averaged OR based on these studies is 1.067.

Table 89.
Association between UPDRS III and falls frequency: Odds ratio – data included in the analysis

Study	Falls frequency – odds ratio per 1 point increase in UPDRS III	
	Mean	**N**
Ashburn 2001	1.09	57
Kataoka 2011	1.06	30
Contreras 2012	1.06	160
Average	**1.067**	**247**

A summary of final assumptions of the analysis with regard to falls is presented in the table below.

Table 90
Data on falls in PD – model input data

Parameter	Value	
	Mean	**SD**
Percentage of patients who experience falls [a]	42.78%	0.92%
Annual number of falls per faller [a]	1	-
Percentage of injurious falls (= falls requiring hospitalization) [a]	50.88%	2.48%
Average annual probability of fall requiring hospitalization [a]	**21.77%**	**-**
OR for falls frequency per 1 point increase in UPDRS III [b]	1.067	0.031

a) parameters estimated for patients with average UPDRS III value of 12 (reference value for application of OR)
b) UPDRS III value of 12 as reference (increased/decreased falls frequency for UPDRS III scores above/below 12)

B.7. Mortality

Mortality rates in the model are based on UK Life Tables for the general population, and adjustments for more advanced patients (defined through UPDRS III), based on data identified in the literature review (A.4).

B.7.1. Life tables

National Life Tables (United Kingdom 2012-2014) for general adults population in UK are presented in Table 91. Additionally, for illustrative purposes, estimated percentage of males and average death probability for the cohort of patients included in the base-case analysis (age = 52.5, proportion of males = 71.3%) is shown.

Table 91.
UK life tables for general adult population

Age	Death probability		Proportion of males in PD group	Average death probability
	Males	Females		
18	0.000443	0.000183	-	-
19	0.000477	0.000198	-	-
20	0.000467	0.000202	-	-
21	0.000473	0.000207	-	-
22	0.000468	0.000214	-	-
23	0.000555	0.000232	-	-
24	0.000521	0.000227	-	-
25	0.000559	0.000255	-	-
26	0.000641	0.000259	-	-
27	0.000620	0.000274	-	-
28	0.000627	0.000343	-	-
29	0.000709	0.000321	-	-
30	0.000755	0.000370	-	-
31	0.000793	0.000422	-	-
32	0.000796	0.000424	-	-
33	0.000875	0.000469	-	-
34	0.000924	0.000538	-	-
35	0.001016	0.000564	-	-
36	0.001047	0.000600	-	-
37	0.001176	0.000635	-	-
38	0.001355	0.000732	-	-
39	0.001420	0.000822	-	-

Age	Death probability		Proportion of males in PD group	Average death probability
	Males	Females		
40	0.001576	0.000883	-	-
41	0.001626	0.000957	-	-
42	0.001690	0.001058	-	-
43	0.001882	0.001156	-	-
44	0.002062	0.001270	-	-
45	0.002248	0.001382	-	-
46	0.002360	0.001446	-	-
47	0.002502	0.001622	-	-
48	0.002677	0.001710	-	-
49	0.002940	0.001924	-	-
50	0.003101	0.002156	-	-
51	0.003423	0.002344	-	-
52	0.003702	0.002558	71.3%	0.00337
53	0.004067	0.002780	71.3%	0.00370
54	0.004528	0.002977	71.3%	0.00408
55	0.004865	0.003402	71.2%	0.00444
56	0.005353	0.003674	71.2%	0.00487
57	0.005962	0.004033	71.2%	0.00541
58	0.006607	0.004385	71.1%	0.00597
59	0.007416	0.004772	71.1%	0.00665
60	0.008002	0.005226	71.0%	0.00720
61	0.008809	0.005808	71.0%	0.00794
62	0.009679	0.006283	70.9%	0.00869
63	0.010340	0.006755	70.8%	0.00929
64	0.011306	0.007356	70.8%	0.01015
65	0.012111	0.007936	70.7%	0.01089
66	0.013191	0.008579	70.6%	0.01183
67	0.014606	0.009639	70.5%	0.01314
68	0.016131	0.010748	70.4%	0.01454
69	0.017970	0.011719	70.3%	0.01611
70	0.019796	0.013122	70.1%	0.01780
71	0.022073	0.014429	70.0%	0.01978
72	0.025273	0.016475	69.8%	0.02262
73	0.027243	0.018281	69.6%	0.02452
74	0.029995	0.020211	69.5%	0.02701
75	0.033205	0.022532	69.2%	0.02992

Age	Death probability		Proportion of males in PD group	Average death probability
	Males	Females		
76	0.036573	0.025116	69.0%	0.03302
77	0.040211	0.028226	68.8%	0.03647
78	0.045461	0.031273	68.5%	0.04099
79	0.049611	0.035843	68.2%	0.04523
80	0.056322	0.040816	67.9%	0.05134
81	0.063280	0.045772	67.5%	0.05759
82	0.071519	0.051697	67.1%	0.06500
83	0.079828	0.058965	66.6%	0.07286
84	0.089056	0.067661	66.1%	0.08181
85	0.100248	0.076098	65.6%	0.09194
86	0.111772	0.085623	65.0%	0.10262
87	0.123954	0.096404	64.3%	0.11413
88	0.137712	0.106974	63.6%	0.12653
89	0.152512	0.122022	62.8%	0.14117
90	0.166455	0.136144	62.0%	0.15493
91	0.182981	0.151001	61.1%	0.17055
92	0.208161	0.171558	60.2%	0.19360
93	0.222733	0.185224	59.1%	0.20740
94	0.231918	0.202300	58.0%	0.21947
95	0.259055	0.219153	57.1%	0.24192
96	0.286001	0.251076	55.8%	0.27055
97	0.308416	0.267500	54.6%	0.28984
98	0.330830	0.289642	53.2%	0.31154
99	0.347717	0.315701	51.7%	0.33224
100	0.355920	0.329873	50.5%	0.34302

B.7.2. Association between UPDRS scores and mortality

According to the results of the meta-analysis by MacLeod 2014, mortality in PD is higher than in the general population. However, studies in early PD stages indicated mortality was not different from the general population (e.g. Peretz 2014, Williams-Gray 2013, Duarte 2013 [294, 307, 315]).

Five out of 22 identified studies in the systematic review (details in section A.4) reported data on the association between UPDRS score and mortality, of which 3 studies reported a correlation between UPDRS III scores and PD-related mortality (Marras 2005, Forsaa 2010 and Skorvanek 2013 [299–301]). Hazard ratios in these trials indicate a relation between a 10-point increase in UPDRS score

and mortality. Marras 2005 study also reported correlation between UPDRS II and UPDRS total score and mortality. Association between total UPDRS (defined as sum of UPDRS I, UPDRS II and UPDRS III) and mortality was also analysed in Vu 2012 . In Oosterveld 2014 study, UPDRS motor scores less than 30 were indicated as predictors of survival.

Based on available data, for predicting increase of mortality associated with disease progression measured by UPDRS, data on UPDRS III scores were used as this was the most frequently reported. Based on results of 3 studies, hazard ratio per 10 points change of UPDRS III scores was calculated – 1.31 (SD 0.094).

Table 92
Association between UPDRS III and mortality – data included in the analysis and model input data

Study	No of patients	Hazard Ratio per 10 points UPDRS III increase	Comment
Marras 2005	800	1.30	associations between baseline variables of interest and time to death
Forsaa 2010	230	1.25	associations between variables with mortality adjustment for age
Skorvanek 2013	153	1.48	only poster for this study was available
Mean	**-**	**1.31**	Weighted by number of patients
SD	**-**	**0.094**	**-**

As higher mortality in PD does not apply to patients at initial stages of disease, in the model the increased risk of mortality predicted by UPDRS scores was added for patients with UPDRS III score above 15 (value chosen arbitrarily).

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